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# EDITORIAL

# Precordial Movements

MUCH VALUABLE clinical information can be obtained by careful palpation of the precordial area. Aside from shocks and thrills, one can frequently feel certain outward motions which constitute a guide to the nature of the underlying disorder of the heart. A sharp distinction should be drawn between forward motions confined to the region of the apex and those felt over the whole left precordial area.

## PALPABLE PRECORDIAL FORWARD MOTION

The *normal apex thrust* is felt in a small area (usually not larger than a 25 cent coin) in a single interspace and is commonly a gentle tap of short duration. A more sustained lift of greater amplitude, palpable over a larger area, is usually found in persons with left ventricular hypertrophy, but may be encountered under several other circumstances.

Following *myocardial infarction*, the apex thrust is often exaggerated and may be indistinguishable from that of patients with hypertrophy of the left ventricle. It is usually easier to recognize such functional apical aneurysms by palpation than by x-ray film. In some patients presenting this phenomenon, the autopsy reveals a classic thin-walled localized aneurysm; in others only the scar of an infarct is seen. It would seem that in such subjects the aneurysmal bulge only appears during pressures comparable to those existing during systole.

Apical bulges may appear during *anginal attacks* and disappear as the pain subsides. Such anginal bulges can be felt in only a minority of patients, but can be recorded in the majority. Between episodes of pain the traces of apical motion are often normal; less frequently, they are somewhat abnormal, but not sufficiently so to produce a detectable alteration by palpation.

There are a few patients with *right ventricular hypertrophy* who have a prominent apex thrust. In most such instances the entire left precordial region will display a similar heave and the apex beat will not be disproportionately exaggerated. Occasionally, it will be impossible to decide by palpation alone whether the patient has hypertrophy of both ventricles or right ventricular hypertrophy of such a marked degree that this chamber includes the apex.

Systolic forward motion of the entire left precordial area may be noted in some healthy young persons with *slender habitus and thin chest walls.* More commonly, this phenomenon, when occurring in subjects without organic disease, is due to anxiety, excitement or exertion. Various extracardiac disorders, such as thyrotoxicosis and severe anemia, which lead to increased activity of the heart, may also produce palpable diffuse precordial forward movement. In these several circumstances, increased cardiac output appears to be the underlying mechanism.

*Right ventricular overload* is another common cause of an exaggerated precordial lift. Eddleman and Thomas have recently shown that when right ventricular output is elevated but pulmonary pressure is normal, as in many patients with atrial septal defects, the increased outward motion is of brief duration, starts during isometric contraction and is soon succeeded by an abnormally large inward motion which appears to be due to the exaggerated stroke volume. However, when there is a pressure load on the right ventricle, the forward thrust is sustained throughout systole and is interrupted only by a small inward motion during ejection. In most instances, the diagnosis of increased

right ventricular work may be readily made by simple palpation, which is often a more sensitive guide than either the electrocardiogram or the x-ray film. However, in order to distinguish between pressure loads and flow loads, instrumental methods are frequently necessary.

The exaggerated forward parasternal lift is apparently related mainly to load rather than to hypertrophy of the right ventricle because it is often observed to disappear during treatment of congestive heart failure.

The differentiation between exaggerated precordial motions due to increased cardiac output and those due to excessive right ventricular load cannot always be made by palpation. However, in many such instances, palpation of the radial pulse combined with blood pressure measurement will suffice to settle the question. The presence of a full and bounding (pseudo-Corrigan) pulse with a high pulse pressure points toward increased cardiac output, while a small pulse with a low pulse pressure speaks for right ventricular stress as the cause of the exaggerated diffuse precordial lift.

Certain patients with *myocardial infarction* display precordial bulges. When these are of small magnitude they require instrumental detection, but the larger bulges can be recognized by palpation. In some patients the abnormal precordial movements appear at an early time after the onset when the electrocardiogram is still normal.

Although there is not complete agreement between the site of the bulge and the area of the infarct, as indicated by the electrocardiogram, there is a general parallelism. Thus anteroseptal infarctions are commonly associated with a large forward motion in the lead $V_2$ and $V_3$ regions in the third, fourth and fifth interspaces. Similar bulges are sometimes felt in persons with electrocardiographic evidence of posterior infarction, and are possibly due to systolic forward displacement of the posterior part of the septum into the right ventricle. Subjects with posterior infarction may also display bulges in the upper epigastrium. Palpation alone will usually not distinguish between infarction and right ventricular stress as the cause of a diffuse precordial heave.

Mention has already been made of those exceptional instances of right ventricular hypertrophy which are associated with exaggeration of the apex thrust. This may lead to the erroneous idea that the left ventricle is also hypertrophied. The opposite situation is occasionally observed. Thus a person with well marked *left ventricular hypertrophy* may have, in addition to the typical prominent and sustained apex beat, a pronounced diffuse precordial heave. This is possibly due to forward displacement of the septum during systole by the greatly thickened free wall of the left ventricle. Both of these confusing situations tend to occur only when the hypertrophy is of high degree. Under these circumstances the electrocardiogram or the x-ray film will usually supply trustworthy information. It is when the hypertrophy is less pronounced that these tools are unreliable and palpation is likely to be the more accurate guide.

The conditions which produce increased palpable forward motion may be summarized as follows: (1) *An exaggerated apex thrust:* (a) left ventricular hypertrophy; (b) apical ischemia due to infarction or to an anginal attack; and (c) exceptional instances of marked right ventricular hypertrophy. (2) *A diffuse precordial lift,* usually more marked in the left parasternal region than at the apex: (a) increased cardiac output whether due to physiologic or pathologic conditions; (b) right ventricular stress; (c) myocardial infarction; and (d) a few instances of pronounced left ventricular hypertrophy.

## The Kinetocardiogram

For some years we have been recording precordial movements and have designated such traces as kinetocardiograms. The pattern of movements in a given area is quite similar in different healthy subjects and is entirely different in the right and left parasternal regions. Tracings from the latter area resemble those from the apex in most normal subjects. The kinetocardiogram allows recording of the various movements in relation to the electrocardiogram, heart sounds, carotid pulse, ballistocardiogram and various other circulatory functions. The tracings will frequently display the typical motions of hypertrophy, infarctional or ischemic bulge, etc., when the movements are not large enough to be detected by palpation. Other types of information which these records may provide are as follows:

(1) *Patients with myocardial failure* nearly always exhibit a relative exaggeration of atrial motions (i.e., of deflections starting about 0.06 second after the start of the P wave) as compared to ventricular movements. Improvement, whether produced by digitalis or other measures, is usually associated with a change toward

normal in this ratio. These statements are based on data currently being assembled for publication by Skinner.

(2) *During anginal attacks* some, but not all, patients display a similar relative exaggeration of atrial movement (unpublished data of Liebskind, Phillips and Skinner). It appears that in these patients, as in those with congestive failure, the ventricular Starling curve is grossly abnormal but the atrial curves are still such that a slight rise in pressure produces a large increase in the force of contraction.

(3) *Mitral stenosis* with regular rhythm is usually characterized by an abnormally large backward atrial motion which disappears when fibrillation develops. At times this movement, which is presumably due to an exaggerated backward pull by the left atrium, may be of value in differentiating mitral stenosis from cor pulmonale in a patient with a doubtful or absent diastolic rumble.

(4) Most of the published data on the *practical application* of the kinetocardiogram are to be found in the papers of Eddleman and his co-workers.[1–3] Among their significant findings are: (a) the demonstration of a parallelism between clinical and kinetocardiographic improvement following operation for mitral stenosis; (b) the delineation of characteristic and different patterns for mitral stenosis and for mitral insufficiency and (c) the finding of a progressive type of abnormality in patients with increasing degrees of functional impairment due to aortic insufficiency.

(5) Recent (and as yet unpublished) observations of Eddleman and Thomas offer strong evidence that a high degree of parallelism exists between pulmonary vascular resistance and the ratio of the outward to the inward systolic movement in the right parasternal area. Should this relationship be confirmed by further investigations its importance will be obvious.

The precordial movements are numerous and highly complex. The exact nature of the cardiac events responsible for most of them is only now being studied. The effects of such physiologic variables as age and posture have not been clarified in detail. The limits of normality remain to be defined. We do not as yet know the optimal methods of recording these deflections or whether they represent displacement or its derivative. Despite these shortcomings the study of such records has already taught us to palpate more effectively and has yielded other information of certain limited practical value. The ultimate place of the kinetocardiogram as an investigative or diagnostic tool will probably not be established until a number of years have passed.

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# Clinical Studies

## The Changes in Right and Left Heart Pressures During Exercise and Recovery in Rheumatic Heart Disease*

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EVALUATION of cardiovascular performance in man, both at rest and during exercise, by the technic of right heart catheterization has become commonplace in the past decade.[1–5] Most reports have presented data at rest and at one point in exercise. A few investigators have analyzed the variations in right heart pressures during different exercise and recovery periods.[6,7]

The purpose of the present paper is to examine the changes in right heart pressures during successive exercise and recovery periods, and to extend this type of observation to the left heart by means of right and combined right and left heart catheterization.[8]

### MATERIAL AND METHODS

Forty patients with mitral valve disease were studied. Multivalvular disease was noted in a few subjects. The physical characteristics and diagnoses are given in Table I. The methods of clinical and physiologic study have been presented elsewhere.[8,9] Right and left heart pressures were recorded at rest supine, at rest supine with the legs elevated in stirrups, at various exercise periods and at the onset of recovery with the legs still elevated, as well as subsequent recovery periods with the legs flat on the fluoroscopic table. The data for pulmonary artery and right ventricular pressures in Tables II and III were obtained during right heart catheterization alone; left atrial and ventricular pressures were recorded during combined right and left heart catheterization.

### RESULTS

The variations in pulmonary artery mean pressure at rest and during exercise and recovery are illustrated in Table II. The data have been divided into six groups based upon the control level of pulmonary artery pressure, the rhythm (sinus rhythm or atrial fibrillation) and the operative status. Three patterns of elevation in pulmonary artery mean pressure during exercise have emerged. (1) The most frequent (group A, Case 9) is that of an initial elevation in pressure, reaching a maximum in the first three minutes of exercise and then leveling off for the remainder of the exercise period. (2) A progressive rise in pulmonary artery mean pressure throughout the exercise period was observed on occasion (group D, Case 22). (3) An early elevation in mean pulmonary artery pressure, followed by a subsequent decrease while exercise was continued, was noted in a few subjects (group B, Case 17). These varied responses were noted in all six groups. In a few patients a significant pressure rise, defined as an elevation of more than 5 mm. Hg, did not develop during exercise.

Several other observations can be made from

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TABLE I

Physical Characteristics and Diagnosis in Forty Cases of Mitral Valve Disease

| Dates of Catheterization | Case No., Sex and Age (yr.) | Body Surface Area ($M.^2$) | Diagnosis* | Comment |
|---|---|---|---|---|
| 1/12/56 | 1, F, 27 | 1.43 | Rh. H. D., E. H., M. I., M. S., A. F., IIIC | Predominant mitral insufficiency; digitalized |
| 1/26/56 | 2, M, 40 | 1.63 | Rh. H. D., E. H., M. I., M. S., A. I., A. S., A. F., IIID | Digitalized |
| 2/9/56 | 3, F, 40 | 1.65 | Rh. H. D., E. H., M. S., N. S. R., Graham Steell murmur, IIIC | Digitalized; mitral insufficiency produced at commissurotomy 2/21/56 |
| 3/31/56 | | 1.61 | | |
| 2/21/57 | | 1.66 | | |
| 2/23/56 | 4, F, 37 | 1.57 | Rh. H. D., E. H., M. S., A. I., N. S. R., IIIC | Digitalized; refused surgery |
| 2/28/56 | 5, F, 34 | 1.71 | Rh. H. D., E. H., M. I., M. S., A. F., IIC | 4 yr. after mitral commissurotomy; digitalized |
| 10/4/56 | | 1.67 | | |
| 3/22/56 | 6, F, 28 | 1.60 | Rh. H. D., E. H., M. S., N. S. R., IIC | Mitral commissurotomy in Detroit, 1951 and 1955; digitalized |
| 4/5/56 | 7, M, 49 | 1.88 | Rh. H. D., E. H., M. S., M. I., A. F., IIC | Predominant mitral insufficiency; digitalized |
| 6/6/57 | | 1.93 | | |
| 4/12/56 | 8, F, 32 | 1.56 | Rh. H. D., E. H., M. S., N. S. R., IIC | Mitral commissurotomy 5/3/56; digitalized |
| 6/2/56 | | 1.49 | | |
| 7/12/56 | | 1.52 | | |
| 4/23/57 | | 1.55 | | |
| 4/14/56 | 9, F, 46 | 1.73 | Rh. H. D., E. H., M. S., N. S. R., IIC | Refused surgical intervention; died suddenly about 2 mo. later; digitalized |
| 4/26/56 | 10, M, 40 | 1.67 | Rh. H. D., E. H., M. S., N. S. R., Graham Steell murmur, IIIC | Mitral commissurotomy 5/22/56; digitalized |
| 6/28/56 | | 1.61 | | |
| 3/14/57 | | 1.73 | | |
| 5/26/56 | 11, F, 54 | 1.50 | Rh. H. D., E. H., M. S., N. S. R., IIC | Digitalized |
| 7/19/56 | | 1.49 | | |
| 6/11/56 | 12, M, 48 | 1.67 | Rh. H. D., E. H., M. S., A. F., IIIC | Mitral commissurotomy 6/27/56; digitalized; not improved postoperatively |
| 6/18/56 | | | | |
| 6/21/56 | 13, F, 37 | 1.66 | Rh. H. D., E. H., M. S., N. S. R., IIC | Mild non-obstructive pulmonary emphysema present; digitalized |
| 1/10/57 | | 1.80 | | |
| 7/5/56 | 14, F, 30 | 1.63 | Rh. H. D., E. H., M. S., N. S. R., IIC | Mitral commissurotomy 9/25/56; digitalized |
| 10/24/56 | | 1.55 | | |
| 9/17/56 | 15, M, 34 | 1.94 | Rh. H. D., E. H., M. S., minimal M. I., A. F., IIIC | Mitral commissurotomy 10/3/56; digitalized |
| 12/6/56 | | 1.94 | | |
| 9/20/56 | 16, F, 48 | 1.50 | Rh. H. D., E. H., M. S., N. S. R., Graham Steell murmur, IIIC | Mitral commissurotomy 11/9/56; digitalized; died 1 mo. postoperatively with bacterial endocarditis |
| 9/23/56 | 17, F, 49 | 1.58 | Rh. H. D., E. H., M. I., M. S., A. I., IIID | Predominant mitral insufficiency; digitalized |
| 10/1/56 | 18, M, 34 | 1.76 | Rh. H. D., E. H., M. S., minimal M. I., A. F., C. H. F., Graham Steell murmur, IIID | Mitral commissurotomy in Boston 12/11/50; probable restenosis of mitral valve; digitalized; refused surgery second time; died 4 mo. later; digitalized |
| 10/18/56 | 19, M, 32 | 1.96 | Rh. H. D., E. H., A. S., A. I., M. S., S. B., IB | Digitalized; minimal symptomatology |
| 10/23/56 | | 1.94 | | |
| 11/1/56 | 20, F, 33 | 1.66 | Rh. H. D., E. H., M. S., A. F., IIC | Previous arterial emboli; mitral commissurotomy 11/28/56; digitalized |
| 1/24/57 | | 1.64 | | |

* See footnote on page 432.

TABLE I (*Continued*)

| Dates of Catheterization | Case No., Sex and Age (yr.) | Body Surface Area ($M.^2$) | Diagnosis* | Comment |
|---|---|---|---|---|
| 11/5/56 | 21, M, 28 | 1.86 | Rh. H. D., E. H., M. I., M. S., A. I., A. F. | Predominant mitral insufficiency; digitalized |
| 11/8/56 | 22, M, 49 | 1.62 | Rh. H. D., As. H. D., E. H., M. S., old ant. wall myocardial infarction, A. F., IIID | Mitral commissurotomy 11/19/56; died 2 days postoperatively; digitalized |
| 11/15/56 | 23, F, 49 | 1.68 | Rh. H. D., E. H., M. I., M. S., A. F., IVD, essential hypertension | Predominant mitral insufficiency; digitalized |
| 11/20/56 | 24, F, 49 | 1.52 | Rh. H. D., E. H., M. S., M. I., A. I., A. F., IIIC | Left ventricular hypertrophy on E.C.G. and fluoroscopy; digitalized |
| 11/29/56<br>7/6/57 | 25, M, 34 | 1.73<br>1.66 | Rh. H. D., E. H., M. S., A. F., IIIC | Mitral commissurotomy 6/4/57; digitalized; recurrent tachycardia postoperatively |
| 12/6/56<br>1/3/57 | 26, F, 37 | 1.56<br>1.52 | Rh. H. D., E. H., M. S., N. S. R., IB | Mitral commissurotomy in Jan. 1956; digitalized after first catheterization |
| 12/27/56<br>1/17/57<br>2/7/57 | 27, M, 21 | 1.59<br>1.60<br>1.60 | Rh. H. D., E. H., M. S., N. S. R., IIC | Mitral commissurotomy 2/13/57; digitalized between first two studies |
| 12/29/56 | 28, M, 28 | 1.82 | Rh. H. D., E. H., M. S., M. I., A. I., A. F., IVD | Predominant mitral insufficiency; digitalized |
| 2/7/57 | 29, F, 53 | 1.41 | Rh. H. D., E. H., M. S., minimal A. S., A. F., IIC | Systemic arterial emboli; digitalized; on long term anticoagulants |
| 2/14/57 | 30, F, 59 | 1.52 | Rh. H. D., E. H., M. S., M. I., A. F., IIIC | Mitral commissurotomy 2 yr. earlier; digitalized |
| 3/4/57<br>5/20/57 | 31, F, 30 | 1.46<br>1.46 | Rh. H. D., E. H., M. S., N. S. R., IB | Asymptomatic; not digitalized |
| 4/9/57 | 32, M, 42 | 1.85 | Rh. H. D., E. H., M. S., N. S. R., Graham Steell murmur, IIID | Apical diastolic murmur not heard; digitalized |
| 5/2/57 | 33, F, 49 | 1.55 | Rh. H. D., E. H., M. S., A. F., IIIC | Mitral commissurotomy 7/11/57; digitalized |
| 5/9/57 | 34, F, 48 | 1.50 | Rh. H. D., E. H., M. S., A. F., Graham Steell murmur, IIID | Mitral commissurotomy 5/13/57; digitalized |
| 6/10/57 | 35, M, 33 | 2.13 | Rh. H. D., E. H., M. S., Graham Steell murmur, IIC | Mitral commissurotomy 6/25/57; not digitalized |
| 6/18/57 | 36, M, 36 | 1.87 | Rh. H. D., E. H., M. S., N. S. R., L. B. B. B., IIC | Myocardial factor primary; digitalized |
| 7/2/57 | 37, F, 42 | 1.90 | Rh. H. D., E. H., M. S., A. F., IIC | Mitral commissurotomy 11/10/57; digitalized |
| 7/15/57<br>7/22/57 | 38, M, 31 | 1.78<br>1.76 | Rh. H. D., E. H., M. S., minimal M. I., N. S. R., Graham Steell murmur, IIC | Mitral commissurotomy 9/10/57; digitalized after first study; minimal mitral insufficiency first noted at surgery |
| 9/3/57 | 39, F, 37 | 1.38 | Rh. H. D., E. H., M. S., N. S. R., IA | Asymptomatic; not digitalized |
| 10/21/57<br>10/30/57 | 40, F, 35 | 1.74<br>1.71 | Rh. H. D., E. H., A. I., M. I., N. S. R., IIC | Left ventricular enlargement; digitalized after first study |

* Rh. H. D. = rheumatic heart disease. E. H. = enlarged heart. M. S. = mitral stenosis. M. I. = mitral insufficiency. A. I. = aortic insufficiency. A. S. = aortic stenosis. N. S. R. = normal sinus rhythm. A. F. = atrial fibrillation. As. H. D. = arteriosclerotic heart disease. S. B. = sinus bradycardia. R. B. B. B. = right bundle branch block. L. B. B. B. = left bundle branch block.

TABLE II
Pulmonary Artery Mean Pressures at Rest, and During Exercise and Recovery

| Case No. | Rest | Legs Up | Exercise | | | | Recovery | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Onset | 1 Min. | 2–3 Min. | 4–18 Min. | Onset | 1 Min. | 2 Min. | 3–4 Min. | 5–10 Min. | 11–30 Min. |
| **A. Preoperative Resting Pressures 30 or More mm. Hg: Normal Sinus Rhythm** | | | | | | | | | | | | |
| 3 | 42 | .. | 60 | .. | .. | 77 | 77 | 59 | .. | .. | 45 | 45 |
| 4 | 32 | 38 | 39 | 36 | 37 | 30 | 29 | 31 | 28 | .. | .. | 30 |
| 9 | 32 | 35 | 42 | 54 | 51 | 55 | 50 | .. | 35 | 34 | 33 | 32 |
| 10 | 42 | 42 | 46 | 52 | 53 | 57 | 55 | 41 | .. | 40 | 41 | 41 |
| 14 | 34 | 34 | 46 | 49 | 50 | 61 | 53 | 42 | 37 | .. | 36 | 30 |
| 16 | 56 | 76 | 87 | 101 | 103 | 109 | .. | 96 | .. | 90 | .. | 69 |
| 38 | 30 | 39 | 50 | 55 | 53 | 48 | 44 | 36 | .. | 32 | 31 | 34 |
| 38 | 30 | 36 | 46 | .. | .. | 47 | 41 | .. | .. | 32 | 31 | 34 |
| **B. Preoperative Resting Pressure 30 or More mm. Hg: Atrial Fibrillation** | | | | | | | | | | | | |
| 1 | 31 | .. | 32 | .. | 41 | 44 | 38 | .. | .. | 33 | 29 | 30 |
| 2 | 33 | .. | 41 | 48 | .. | 54 | .. | .. | 36 | .. | 33 | 32 |
| 17 | 35 | 40 | 56 | 61 | 63 | 55 | 52 | 49 | .. | 46 | 38 | 34 |
| 21 | 36 | 39 | 43 | 52 | 54 | 54 | 56 | 42 | .. | 42 | 39 | 37 |
| 28 | 34 | 40 | 44 | 46 | 48 | 54 | 54 | 46 | .. | 41 | 39 | 38 |
| **C. Preoperative Resting Pressure Less Than 30 mm. Hg: Normal Sinus Rhythm** | | | | | | | | | | | | |
| 8 | 26 | 31 | 49 | 59 | 60 | 57 | 57 | 40 | .. | 35 | 29 | 26 |
| 11 | 14 | 17 | 21 | 24 | 24 | 23 | 19 | 15 | .. | 13 | .. | 12 |
| 13 | 12 | 11 | 14 | .. | 13 | .. | .. | 13 | 8 | .. | 10 | 11 |
| 13 | 13 | 12 | 14 | 17 | 17 | 16 | 13 | 9 | 9 | .. | 8 | 9 |
| 19 | 22 | 29 | 33 | 31 | 34 | 32 | 29 | .. | 28 | .. | 25 | 23 |
| 19 | 20 | 22 | 23 | 28 | 31 | .. | .. | .. | 20 | 18 | 19 | 20 |
| 27 | 26 | 31 | .. | 44 | 46 | 47 | 46 | 35 | .. | 35 | 27 | .. |
| 27 | 17 | 20 | .. | 26 | 26 | 29 | 24 | .. | 18 | .. | 17 | 16 |
| 27 | 21 | 23 | .. | 31 | 31 | 40 | .. | 30 | .. | 26 | .. | 25 |
| 31 | 16 | 15 | 23 | 29 | 31 | 28 | 22 | 13 | .. | .. | 14 | 13 |
| 39 | 13 | 12 | 16 | 25 | .. | .. | 20 | 16 | .. | 8 | 8 | 8 |
| 40 | 10 | 12 | 17 | 16 | 18 | 12 | 11 | .. | .. | 6 | 6 | 7 |
| **D. Preoperative Resting Pressure Less Than 30 mm. Hg: Atrial Fibrillation** | | | | | | | | | | | | |
| 7 | 28 | 32 | 36 | .. | 42 | 41 | 39 | .. | 29 | .. | .. | 28 |
| 12 | 21 | 26 | 28 | .. | 30 | 28 | 22 | .. | .. | 20 | 19 | .. |
| 12 | 20 | 24 | 28 | 25 | 29 | 27 | 24 | 17 | .. | 17 | 19 | .. |
| 15 | 27 | 34 | 39 | 48 | 53 | 57 | 56 | 46 | 40 | .. | .. | 34 |
| 20 | 21 | 22 | 24 | 27 | 29 | 33 | 29 | .. | .. | .. | 19 | 20 |
| 22 | 27 | 27 | 34 | 38 | 44 | 56 | 55 | 45 | .. | 36 | 31 | 28 |
| 25 | 24 | 28 | .. | 42 | 40 | 44 | .. | .. | .. | 21 | .. | 17 |
| 29 | 21 | 25 | 24 | 26 | 29 | 29 | .. | 21 | .. | 18 | 16 | .. |
| 37 | 19 | 33 | .. | 58 | .. | .. | .. | .. | 33 | .. | 26 | 20 |
| **E. Postoperative Studies: Normal Sinus Rhythm** | | | | | | | | | | | | |
| 3 | 37 | 50 | 55 | 57 | 61 | 50 | 48 | .. | 41 | .. | 38 | 41 |
| 3 | 39 | 62 | 66 | 77 | 84 | 79 | .. | 52 | .. | 43 | 40 | 38 |
| 6 | 20 | 21 | 26 | .. | 31 | 30 | .. | .. | .. | 22 | 21 | 21 |
| 8 | 16 | 19 | 22 | 26 | 25 | 24 | 19 | 16 | .. | 15 | .. | 14 |
| 8 | 15 | 15 | 19 | 20 | 19 | 18 | 16 | 13 | .. | 13 | 13 | 14 |
| 8 | 10 | 11 | 14 | 15 | 16 | 14 | 13 | 10 | .. | 9 | 9 | 9 |
| 10 | 30 | 33 | 36 | 38 | 40 | 42 | 42 | 39 | .. | 32 | 32 | 32 |
| 10 | 19 | 18 | 20 | 23 | 25 | 30 | 29 | .. | .. | .. | .. | 19 |
| 14 | 18 | 19 | 23 | 24 | 25 | .. | .. | .. | .. | .. | 14 | 14 |
| 26 | 15 | 22 | 25 | 25 | 23 | 20 | 16 | 13 | .. | 12 | 11 | 12 |
| 26 | 17 | 16 | 21 | 23 | 24 | 24 | 18 | 15 | .. | 14 | 14 | 14 |
| **F. Postoperative Studies: Atrial Fibrillation** | | | | | | | | | | | | |
| 5 | 14 | .. | 16 | 17 | 18 | 17 | 15 | .. | 12 | 12 | .. | 13 |
| 5 | 11 | 14 | 15 | 17 | 17 | 16 | 14 | 11 | 11 | .. | 10 | 12 |
| 15 | 23 | 25 | 29 | 34 | 39 | 41 | 40 | 32 | 29 | .. | 28 | 23 |
| 18 | 42 | 46 | 50 | 53 | 57 | 75 | 73 | 64 | 59 | .. | .. | 49 |
| 20 | 16 | 16 | 18 | 19 | 19 | 19 | 17 | .. | 14 | .. | 13 | 14 |
| 23 | 32 | 31 | 35 | 46 | 48 | .. | 55 | .. | .. | .. | 44 | 32 |
| 25 | 17 | .. | 28 | 30 | 33 | 39 | .. | 20 | .. | 18 | 16 | 11 |
| 30 | 16 | 17 | 20 | 21 | 23 | 27 | 22 | .. | 17 | .. | 16 | .. |

Table II. The first is that elevation of the lower extremities is *per se* frequently associated with an increase in mean pulmonary artery pressure. The second is that the pressure at eleven to thirty minutes of recovery may on occasion be lower than the initial resting control values. The third is that pressures have often returned to control levels at five to ten minutes of recovery. Significant continued elevation of pulmonary artery pressure after thirty minutes of recovery is an unusual finding.

The patterns of increase in pulmonary artery pulse pressure during exercise also fall into three categories as did the increase in mean pressure. The most frequent response is that of an initial elevation in pulse pressure, reaching a maximum in the first three minutes of exercise and then leveling off for the remainder of the exercise period. An initial elevation in pulse pressure, followed by a fall as exercise continued, and a progressive elevation in pulse pressure throughout exercise were also observed.

The changes in right ventricular end-diastolic pressure during exercise and recovery are outlined in Table III. Right ventricular failure, as defined by a gross elevation in right ventricular end-diastolic pressure above 5 mm. Hg, was observed in a number of subjects, even in patients with a control mean pulmonary artery pressure less than 30 mm. Hg. In contrast, significant elevation in left ventricular end-diastolic pressure during exercise was observed in only one patient with mitral valve disease. This man is a probable example of the myocardial factor in mitral stenosis (Case 36).

Table IV illustrates the progressive changes in the left atrial-left ventricular mean diastolic gradient during exercise and recovery. The most frequently observed pattern of gradient increase during exercise is a gradient increment reaching a maximum value at two to three minutes and then leveling off (group B, Case 24) at a constant level. A progressive increase in gradient magnitude throughout exercise was not commonly observed (group D, Case 29).

The variations in left atrial mean pressure during exercise are shown in Table V. Again two patterns of pressure increment during exercise are noted. (1) In the more frequently observed response there is an initial increment in left atrial mean pressure to a maximum level at two to three minutes; no further elevation is noted during the remainder of the exercise period (group B, Case 24). (2) The less common response is one of progressive increase in left atrial mean pressure throughout exercise (group D, Case 29).

## Comments

Pulmonary artery pressure in patients with rheumatic mitral valve disease varies with certain relatively well recognized factors such as the size of the mitral valve orifice, the status of the left ventricular myocardium, left atrial pressure, cardiac output, ventricular rate and the presence or absence of a pulmonary vascular pathologic condition such as atherosclerosis or possibly active vasoconstriction. The quantitative importance of factors such as intrapleural pressure, pulmonary blood volume and bronchomotor tone is less clearly established. It is not feasible to measure simultaneously cardiac output, pulmonary artery pressure and ventricular rate throughout exercise and recovery. The pulmonary artery pressures shown in Table II are therefore the resultant of the interaction of a number of factors.

Ferrer et al.[6] and Donald and co-workers[7] have previously studied the variations in pulmonary artery pressure during successive exercise periods in patients with rheumatic heart disease. Ferrer reported data in fourteen patients. In eight subjects the rise in pulmonary artery mean pressure reached a plateau in the first few minutes of exercise and then remained constant throughout the remainder of the exercise period. In three subjects an initial rise and a subsequent fall in mean pressure was noted as exercise continued; in three patients the last pressure measurements during exercise demonstrated a continued rise in pulmonary artery mean pressure. The increase in pulmonary artery pulse pressure followed the same pattern as did the mean pressure increments. Donald investigated the changes in pulmonary artery mean pressure during the first five minutes of exercise in ten patients studied prior and subsequent to mitral commissurotomy. The patterns of change in pulmonary artery pressure were similar to those noted by Ferrer et al. and to those in Table II.

Slonim et al.[10] investigated changes in pulmonary artery pressure in the first six minutes of exercise in five normal subjects. In the first fifteen seconds of exercise, with the legs in an exercise machine, a small mean pressure increment was noted in all five subjects, ranging from 3 to 5 mm. Hg. In two subjects the mean pressure remained constant throughout the remainder of exercise; in three subjects the mean

TABLE III

Right Ventricular End-Diastolic Pressures at Rest, and During Exercise and Recovery

| Case No. | Rest | Legs Up | Exercise | | | | Recovery | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Onset | 1 Min. | 2–3 Min. | 4–18 Min. | Onset | 1 Min. | 2 Min. | 3–4 Min. | 5–10 Min. | 11–30 Min. |
| A. Preoperative Resting Pulmonary Artery Mean Pressure 30 or More mm. Hg: Normal Sinus Rhythm | | | | | | | | | | | | |
| 3 | 2 | .. | .. | .. | .. | 6 | .. | 2 | .. | .. | 2 | 2 |
| 4 | 3 | 4 | 4 | 4 | 4 | 5 | .. | 2 | 3 | .. | .. | 3 |
| 9 | 0 | 0 | 0 | 3 | 2 | 2 | 2 | .. | 0 | 0 | 0 | 0 |
| 10 | 5 | 6 | 7 | 10 | 10 | 11 | 10 | 4 | .. | 5 | 5 | 5 |
| 14 | 2 | 6 | 4 | 4 | 5 | 5 | 4 | 1 | 1 | .. | 1 | 1 |
| 16 | 0 | 2 | 6 | 6 | .. | 9 | .. | 8 | .. | 5 | .. | 3 |
| 38 | 7 | 9 | 11 | 13 | 12 | 11 | 8 | 7 | .. | 5 | 6 | 5 |
| B. Preoperative Resting Pulmonary Artery Mean Pressure 30 or More mm. Hg: Atrial Fibrillation | | | | | | | | | | | | |
| 17 | 2 | 3 | 5 | 6 | 6 | 3 | 2 | 2 | .. | 2 | 1 | 1 |
| 21 | 1 | 0 | 4 | 2 | 2 | 3 | 3 | 2 | .. | 1 | 1 | 1 |
| 28 | 3 | 5 | 6 | 6 | 6 | 7 | 7 | 5 | .. | 5 | 3 | 4 |
| C. Preoperative Resting Pulmonary Artery Mean Pressure Less Than 30 mm. Hg: Normal Sinus Rhythm | | | | | | | | | | | | |
| 8 | 4 | 5 | 6 | 6 | 5 | 4 | 4 | 1 | .. | 2 | 0 | 1 |
| 11 | 2 | 3 | 3 | 3 | 3 | 3 | 3 | 2 | .. | 2 | .. | 1 |
| 13 | 2 | 3 | 3 | .. | 3 | .. | .. | 2 | 2 | .. | 2 | 2 |
| 13 | 2 | 1 | 1 | 1 | 1 | 3 | 0 | 0 | 0 | .. | 0 | 0 |
| 19 | 2 | 3 | 5 | 5 | 5 | 3 | 3 | .. | 2 | .. | 1 | 1 |
| 19 | 0 | 0 | 1 | 1 | 1 | .. | .. | .. | 1 | 1 | 1 | 0 |
| 27 | 2 | 4 | 5 | 3 | 3 | .. | .. | 1 | .. | 1 | 2 | 0 |
| 27 | 1 | 1 | 2 | 3 | 3 | 2 | 2 | 0 | 0 | .. | 0 | 0 |
| 27 | 5 | 5 | 5 | 5 | 5 | 6 | 5 | 2 | .. | 2 | .. | 4 |
| 31 | 4 | 4 | 4 | 5 | 5 | 3 | 2 | 1 | .. | .. | 3 | 3 |
| 39 | 4 | 3 | 4 | 4 | .. | 3 | 2 | .. | .. | −1 | 0 | 0 |
| 40 | 0 | 1 | 1 | 1 | 0 | .. | 1 | 1 | .. | 0 | 0 | 0 |
| D. Preoperative Resting Pulmonary Artery Mean Pressure Less Than 30 mm. Hg: Atrial Fibrillation | | | | | | | | | | | | |
| 7 | 3 | 5 | 11 | .. | 7 | 7 | 3 | .. | 2 | .. | 2 | 1 |
| 12 | 3 | 3 | 3 | .. | 4 | 4 | 2 | .. | .. | 1 | 2 | .. |
| 12 | 2 | 5 | 6 | 6 | 6 | 7 | 4 | 3 | .. | 3 | 3 | .. |
| 15 | 5 | 9 | 12 | 11 | 13 | 12 | 11 | 5 | 5 | .. | .. | 5 |
| 20 | 2 | 2 | 2 | 3 | 3 | 3 | 3 | .. | .. | .. | 1 | 1 |
| 22 | 0 | 1 | 1 | 3 | 4 | 3 | 3 | 2 | .. | 0 | 0 | 0 |
| 25 | −2 | 0 | 0 | 0 | 0 | 0 | −1 | −3 | .. | −3 | .. | −3 |
| 29 | 3 | 4 | 3 | 4 | 3 | 3 | 3 | 1 | .. | 1 | 1 | .. |
| 37 | 3 | 8 | 12 | .. | .. | .. | 10 | .. | 3 | .. | 4 | 2 |
| E. Postoperative Studies: Normal Sinus Rhythm | | | | | | | | | | | | |
| 3 | 3 | 2 | 5 | 10 | 14 | 3 | .. | 3 | 2 | 2 | 1 | 1 |
| 6 | 6 | .. | 7 | .. | 9 | 7 | .. | .. | .. | 5 | 4 | 3 |
| 8 | 2 | 2 | 2 | 4 | 3 | 2 | 0 | 1 | .. | 1 | 1 | .. |
| 8 | 2 | 2 | 2 | 3 | 2 | 3 | 1 | 0 | .. | 0 | 0 | 0 |
| 10 | 5 | 4 | 5 | 8 | 6 | 5 | 5 | 3 | .. | 3 | 3 | 4 |
| 10 | 5 | 5 | 6 | 6 | 6 | 3 | .. | .. | .. | .. | .. | 5 |
| 14 | 3 | 4 | 6 | 5 | 5 | 3 | 4 | .. | 3 | .. | 2 | 3 |
| 26 | 0 | 3 | 2 | 1 | 2 | 0 | −1 | −3 | .. | −2 | −1 | 0 |
| 26 | 0 | 1 | 1 | 1 | 0 | −2 | .. | −2 | .. | −2 | −2 | −2 |
| F. Postoperative Studies: Atrial Fibrillation | | | | | | | | | | | | |
| 5 | 4 | .. | 3 | 3 | 3 | 3 | 1 | .. | 1 | 2 | .. | 2 |
| 5 | 2 | 2 | 2 | 1 | 1 | −1 | 1 | 0 | 1 | .. | 1 | 2 |
| 15 | 2 | 3 | 4 | 5 | 3 | 4 | 2 | 1 | 1 | .. | 1 | 1 |
| 18 | 4 | 6 | 8 | 7 | 9 | 8 | 8 | 5 | 4 | .. | .. | 3 |
| 20 | 2 | 2 | 2 | 3 | 3 | 3 | 3 | .. | .. | .. | 1 | 1 |
| 23 | 0 | 1 | 1 | 1 | 2 | .. | .. | .. | .. | .. | .. | 0 |
| 25 | −2 | 0 | 0 | 0 | 0 | 0 | −1 | −3 | .. | −3 | −2 | −2 |

TABLE IV

Left Atrial-Left Ventricular Mean Diastolic Gradient at Rest, and During Exercise and Recovery

| Case No. | Rest | Legs Up | Exercise | | | | | Recovery | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Onset | 1 Min. | 2 Min. | 3–4 Min. | 6–12 Min. | Onset | 1 Min. | 2 Min. | 3–18 Min. |
| A. Preoperative Resting Gradient 9 or More mm. Hg: Normal Sinus Rhythm | | | | | | | | | | | |
| 8 | 9 | 9 | 12 | .. | 13 | .. | ... | .. | 12 | .. | 9 |
| 14 | 16 | 17 | 16 | 22 | .. | 23 | 24 | 22 | 21 | .. | 19, 18 |
| 32 | 22 | 25 | 25 | 26 | 28 | ..* | 28, 31 | 33 | 29 | .. | 25, 23 |
| 35 | 12 | 11 | 14 | 14 | .. | .. | 15 | 13 | 13 | .. | 15 |
| B. Preoperative Resting Gradient 9 or More mm. Hg: Atrial Fibrillation | | | | | | | | | | | |
| 12 | 11 | 11 | 14 | .. | 13 | 14 | ... | 13 | 10 | .. | 8, 9 |
| 24 | 9 | 10 | 16 | 23 | .. | 21 | 25 | 17 | .. | 11 | 10 |
| 25 | 12 | .. | .. | 20 | 19 | 23 | ... | 16 | 15 | .. | 13, 10 |
| 34 | 9 | 9 | 12 | 18 | .. | 17 | 17 | 15 | 10 | .. | 9, 7 |
| C. Preoperative Resting Gradient Less Than 9 mm. Hg: Normal Sinus Rhythm | | | | | | | | | | | |
| 9 | 6 | .. | .. | .. | 9 | 10 | ... | 8 | .. | .. | 7, 5, 6 |
| 27 | 7 | 5 | 8 | .. | 9 | 9 | 13 | 9 | .. | 6 | 7, 7 |
| 31 | 3 | 3 | 4 | .. | 7 | 6 | 5 | 4 | .. | 1 | 1 |
| 36 | 3 | 3 | 3 | 3 | 4 | .. | 5 | 5 | 2 | .. | 2, 3 |
| D. Preoperative Resting Gradient Less Than 9 mm. Hg: Atrial Fibrillation | | | | | | | | | | | |
| 20 | 7 | 9 | 11 | 11 | 13 | 12 | 12 | 10 | 8 | 9 | 7, 8 |
| 22 | 8 | 9 | 12 | .. | 13 | 14 | 15 | 15 | 13 | .. | 8, 7 |
| 29 | 6 | 6 | 9 | 9 | .. | 13 | 16 | 16 | .. | .. | 8, 5 |
| 33 | 6 | 5 | 6 | .. | 9 | 12 | 14 | .. | .. | .. | 10, 7 |
| E. Postoperative Studies: Normal Sinus Rhythm | | | | | | | | | | | |
| 8 | 1 | 1 | 1 | 2 | .. | .. | 2, 1 | .. | 1 | .. | 1, 0 |
| 10 | 1 | .. | .. | .. | 2 | .. | ... | 4 | .. | .. | 1 |
| 10 | 2 | 2 | 2 | 2 | 3 | .. | 1 | .. | .. | .. | 1, 2 |
| 14 | 3 | 3 | 4 | 4 | .. | 6 | 6 | 3 | .. | 3 | 2 |
| 26 | 3 | 4 | 6 | 8 | 9 | 8 | 7 | 6 | .. | .. | 4, 3 |
| F. Postoperative Studies: Atrial Fibrillation | | | | | | | | | | | |
| 15 | 2 | 2 | .. | 8 | 6 | .. | 6 | 6 | 4 | .. | 2 |
| 20 | 4 | 5 | 4 | 4 | .. | 5 | 4 | .. | .. | 3 | ... |
| 30 | 1 | .. | .. | .. | .. | .. | 2, 4 | .. | .. | .. | 1 |

pressure dropped slightly to a level higher than the resting control values as exercise continued.

Ferrer documented the development of right ventricular failure (as defined by elevation of the right ventricular end-diastolic pressure) in seven of twelve subjects with rheumatic heart disease studied during multiple exercise periods. In most patients the exercise elevation in end-diastolic pressure persisted throughout the exercise period. An initial increase in this pressure level followed by a decrease as exercise continued was noted in some subjects in Ferrer's series and in one patient in Table III.

FACTORS IN CHANGES OF PULMONARY ARTERY PRESSURE

Since there are numerous factors that influence the level of pulmonary artery pressure, it is difficult to ascertain why the exercise increments in pulmonary artery pressure fall into three patterns in patients with rheumatic heart disease. The initial rise in pulmonary artery pressure as the legs are elevated prior to the onset of exercise (an observation also noted by other investigators[10,11]) is probably due to displacement of blood from the periphery into the pulmonary vascular bed. The continued rise

TABLE V

Left Atrial Mean Pressure at Rest, and During Exercise and Recovery

| Case No. | Rest | Legs Up | Exercise | | | | | Recovery | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Onset | 1 Min. | 2 Min. | 3–4 Min. | 6–12 Min. | Onset | 1 Min. | 2 Min. | 3–18 Min. |
| A. Preoperative Resting Gradient 9 or More mm. Hg: Normal Sinus Rhythm | | | | | | | | | | | |
| 8 | 22 | 23 | 30 | .. | 38 | .. | .. | .. | 31 | .. | 22 |
| 14 | 22 | 30 | 34 | 34 | .. | 38 | 39 | 36 | 31 | .. | 25 |
| 32 | 26 | 25 | 27 | 27 | 27 | 29 | 33 | 30 | 31 | .. | 28 |
| 35 | 21 | 21 | 24 | 26 | .. | .. | 31 | 29 | .. | 27 | 26 |
| B. Preoperative Resting Gradient 9 or More mm. Hg: Atrial Fibrillation | | | | | | | | | | | |
| 12 | 23 | 24 | 27 | .. | 29 | 29 | .. | 27 | 26 | .. | 17 |
| 24 | 13 | .. | 21 | 27 | .. | 23 | 27 | 20 | .. | 16 | 17 |
| 25 | 21 | 28 | 36 | 36 | 37 | 37 | 35 | 31 | 25 | .. | 22 |
| 34 | 22 | 22 | 27 | 32 | .. | 29 | 30 | 26 | 23 | .. | 21 |
| C. Preoperative Resting Gradient Less Than 9 mm. Hg: Normal Sinus Rhythm | | | | | | | | | | | |
| 9 | 14 | .. | .. | .. | 26 | 24 | .. | 18 | .. | .. | 13 |
| 27 | 18 | 19 | 22 | .. | 24 | .. | 28 | 24 | .. | 17 | 17 |
| 31 | 16 | 16 | 19 | .. | 21 | 20 | 20 | 20 | .. | 16 | 13 |
| 36 | 15 | 25 | 22 | 25 | 20 | .. | 16 | 16 | 9 | .. | 12 |
| D. Preoperative Resting Gradient Less Than 9 mm. Hg: Atrial Fibrillation | | | | | | | | | | | |
| 20 | 15 | 16 | 19 | 19 | 22 | 20 | 21 | 18 | 13 | 11 | 13 |
| 22 | 19 | 16 | 23 | .. | 23 | 26 | 29 | 27 | 22 | .. | 18 |
| 29 | 18 | 18 | 19 | 24 | .. | 27 | 30 | 29 | .. | .. | 19 |
| 33 | 21 | 22 | 24 | 25 | .. | 28 | 30 | 24 | .. | 22 | 21 |
| E. Postoperative Studies: Normal Sinus Rhythm | | | | | | | | | | | |
| 8 | 6 | 4 | 5 | 6 | 6 | .. | 6 | .. | 5 | .. | 4 |
| 10 | 11 | .. | .. | .. | 14 | .. | .. | 16 | .. | .. | 12 |
| 10 | 10 | 9 | 10 | 8 | 7 | .. | 9 | .. | .. | .. | 7 |
| 14 | 13 | 15 | 15 | 15 | .. | 16 | 15 | 16 | .. | 15 | 14 |
| 26 | 9 | 9 | 12 | 12 | 13 | 11 | 8 | 9 | .. | .. | 3 |
| F. Postoperative Studies: Atrial Fibrillation | | | | | | | | | | | |
| 15 | 14 | 14 | .. | 20 | 19 | .. | 22 | 21 | 18 | .. | 13 |
| 20 | 11 | 13 | 11 | 14 | .. | 16 | .. | .. | .. | 11 | .. |
| 30 | 5 | .. | 7 | 5 | .. | 6 | 7 | 5 | .. | 5 | 6 |

early in exercise may be due to a similar process, i.e., increase in pulmonary blood volume. Ventricular heterodynamism[12] early in exercise, with right ventricular output exceeding left ventricular output, would cause a further rise in pulmonary artery pressure. Re-establishment of equal outputs from the two ventricles later in exercise would stabilize pulmonary artery pressure at a level greater than control values. Continued heterodynamism during exercise would result in a continued increment in pulmonary artery pressure throughout the exercise period. The fall in pulmonary artery pressure noted in some subjects as exercise continues may be caused by a fall in right ventricular output, a more negative intrapleural pressure or perhaps pulmonary vasodilation with the opening of new pulmonary vascular channels. It must be admitted however that all these concepts are theoretical and not subject to experimental verification at this time.

### FACTORS IN LEFT ATRIAL PRESSURE

The changes in left atrial mean pressures and mean diastolic left atrial-left ventricular gradients (Tables IV and V) during exercise fall into

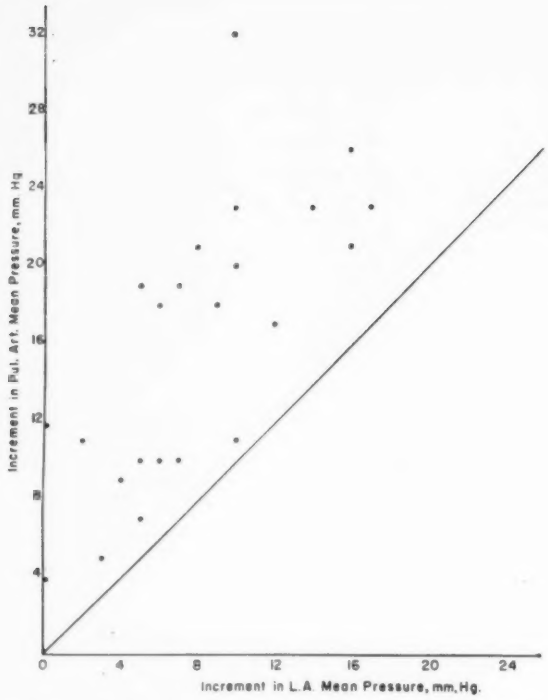


FIG. 1. The maximum exercise increment in pulmonary artery mean pressure (ordinate) is plotted against the maximum rise in left atrial mean pressure (abscissa). The disproportionate elevation in pulmonary artery pressure is readily noted.

two patterns. The first is characterized by an initial increment in pressure to an approximately constant level later during exercise. The second is characterized by a continued increment in left atrial mean pressure and mean atrioventricular diastolic gradient as exercise continues. The first pattern may be ascribed to the increment in flow through a narrowed valve, the second (an uncommon pattern) to an increase in flow plus the effect of tachycardia. Ventricular heterodynamism may also be a factor in producing these changes.

No correlation could be established between the varied patterns of increase in pulmonary artery or left atrial pressures and increases in cardiac output or heart rate during the varied exercise periods. This finding is not unexpected since multiple factors determine these pressures in patients with rheumatic heart disease.

### CORRELATION OF PULMONARY ARTERY AND LEFT ATRIAL PRESSURES

The right heart pressures listed in Tables II and III were obtained during right heart catheterization. Pulmonary artery pressures at rest and during exercise and recovery were also determined simultaneously with left heart pressures during combined right and left heart catheterization in twenty-three patients. In order to determine whether or not these increments in pulmonary artery mean pressure were simply secondary to elevations in left atrial pressure, the maximum exercise increases in left atrial and pulmonary artery mean pressures (exercise minus rest values) are plotted against one another in Figure 1. The increases in pulmonary artery mean pressure are disproportionately greater than those in left atrial mean pressure, all the points falling above a theoretical 45 degree line of identity. This demonstrates that the exercise rise in pulmonary artery pressure is not merely secondary to passive backward transmission of increments in left atrial pressure.

## SUMMARY

The variations in pulmonary artery mean pressure, pulmonary artery pulse pressure, right ventricular end-diastolic and left atrial mean pressures, and the mean diastolic left atrial-left ventricular gradients at rest, and during exercise and recovery have been analyzed. Several distinct patterns of change in these pressures have emerged. The reason for these patterns is not clearly understood. Several possibilities are proposed to explain the observed changes.

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# Hemodynamic Findings in Heart Block with Slow Ventricular Rates*

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THE PURPOSE of this report is to describe cardiovascular dynamics in patients with slow ventricular rates. Six patients with ventricular rates between 26 and 39 per minute were studied by right heart catheterization. Some of these cases were reported on in part by Levinson et al.[1] Four patients had complete heart block and two had second degree atrioventricular block, in all instances secondary to coronary artery disease. Five of the patients were over sixty-two years of age. None had been in clinical heart failure.

In two of these patients with complete heart block, isoproterenol (Isuprel®) was injected into the right ventricle during the course of the catheterization.

## HEMODYNAMIC FINDINGS AT CARDIAC CATHETERIZATION

*Right Atrium:* In all four patients with complete heart block and in one of the two with 2:1 block, the highest right atrial systolic pressure was 8 mm. Hg or more (Table I). The systolic pressure in the right atrium varied from beat to beat and was maximal when the right atrial contraction occurred at or very near the time of closure of the atrioventricular valve. At such times atrial systolic pressures were as much as 11 mm. Hg higher than when the valves were open. These tall *a* waves were transmitted retrograde to the external jugular veins where they appeared as "cannon waves." When atrial contractions occurred after a short ventricular diastole, simultaneously with a premature ventricular contraction, these large atrial systolic waves were not seen (Fig. 1A, Case 6).

The right atrial diastolic pressure varied from −3 to +8 mm. Hg. It tended to rise as ventricular diastole progressed, as shown in Case 2 (Fig. 2).

Carotid sinus pressure in Case 2 led to marked reduction in atrial rate (Fig. 2). As the atrial rate slowed, the atrial pressure rose higher during diastole. With the opening of the A-V valves the atrial pressure dropped to a lower level than in the resting state.

Regurgitant *v* waves of tricuspid insufficiency were not noted in any patient.

*Right Ventricle:* The right ventricular systolic pressures were elevated in all six patients, with the range from 42 to 85 mm. Hg (Table I). The end diastolic pressures ranged as high as 8 mm. Hg.

The right atrial systolic pressure waves were transmitted to the right ventricle and were visible in the intraventricular pressure tracings (Figs. 1A and 1B, Case 6 and Fig. 3A, Case 4). The onset of the atrial systolic pressure waves in the right ventricle in Case 4 occurred from 0.12 to 0.18 second after the onset of the P wave.

Atrial systolic pressures also were recorded simultaneously via a double-lumen catheter in the right ventricle and right atrium. The lag time between appearance of the atrial systolic wave in the atrium and in the ventricle ranged from 0.07 to 0.11 second in Case 1 (Fig. 4) and from 0.06 to 0.12 second in Case 6 (Figs. 1A and 1B).

*Pulmonary Artery: Main Pulmonary Artery:* The systolic pulmonary artery pressures all were elevated, with a range from 42 to 85 mm. Hg (Fig. 5A and Table I). The diastolic pulmonary artery pressures, in contrast to the systolic, were normal (8 to 12 mm. Hg). The pulmonary artery pulse pressures were increased (34 to 63 mm. Hg).

The total pulmonary vascular resistance was

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FIG. 1A. Case 6. Simultaneous electrocardiogram and pressure tracings from the brachial artery, right ventricle and right atrium. The atrial pressure is highest when atrial systole occurs at or near the time of the regular ventricular systoles. Atrial pressure is not as high when atrial systole occurs at the time of premature ventricular systoles.

considerably elevated in all five patients in whom it was calculated (Table I).

Right atrial systolic pressure waves were visible in the main pulmonary artery pressure curves in Cases 3 and 4 (Figs. 7 and 3B, respectively). The atrial systolic pressure waves occurred later in the main pulmonary artery than in the right ventricle in Case 4 (Figs. 3A and 3B).

*Wedged Pulmonary Artery:* The wedged pressure in one instance was remarkable since the rhythm converted spontaneously from 2:1 block to sinus rhythm. With the doubling of ventricular rate, the *a*, *a*, *v* pressure wave pattern (Fig. 6A, Case 5) was replaced by an *a*, *v*, *a*, *v* pressure wave pattern (Fig. 6B, Case 5). The relative heights of the *a* and *v* waves, however, were similar with the 2:1 block and with the sinus rhythm. Occasional ventricular premature beats, which occurred in Case 5, were not associated with significant changes in wedge pressure contour or height (Fig. 6B, Case 5).

*Brachial Artery:* The brachial systolic pressures ranged from 145 to 200 mm. Hg and the diastolic from 51 to 70 mm. Hg (Fig. 5B and Table I). The highest diastolic pressures were recorded in the patient with the most rapid ventricular rate. The brachial artery pulse pressures all were increased (80 to 140 mm. Hg).

The total systemic vascular resistance was considerably elevated in all five patients in whom it was calculated (Table I). Despite this elevation in total systemic vascular resistance, the brachial artery mean pressures all were below normal.[14]

Atrial systolic pressure waves also were seen on the brachial artery pressure curves in Case 3 (Fig. 7), and occurred at a later time than in the pulmonary artery.

*Cardiac Index and Stroke Volume:* The cardiac index ranged from 1.3 to 2.3 L./min./M² BSA (Fig. 8 and Table II).

The stroke volume varied from 56 to 110 cc. per beat and the stroke index from 41 to 85 cc./beat/M² BSA (Table II).

Based on an expected normal cardiac index of 2.5 to 3.0 L./min./M² BSA for people of this age group and heart rate of between 63 and 70 per minute, the stroke volume and stroke index were elevated in all instances but one (Table II). The stroke index ranged from 22 to 118 per cent above normal in five patients,

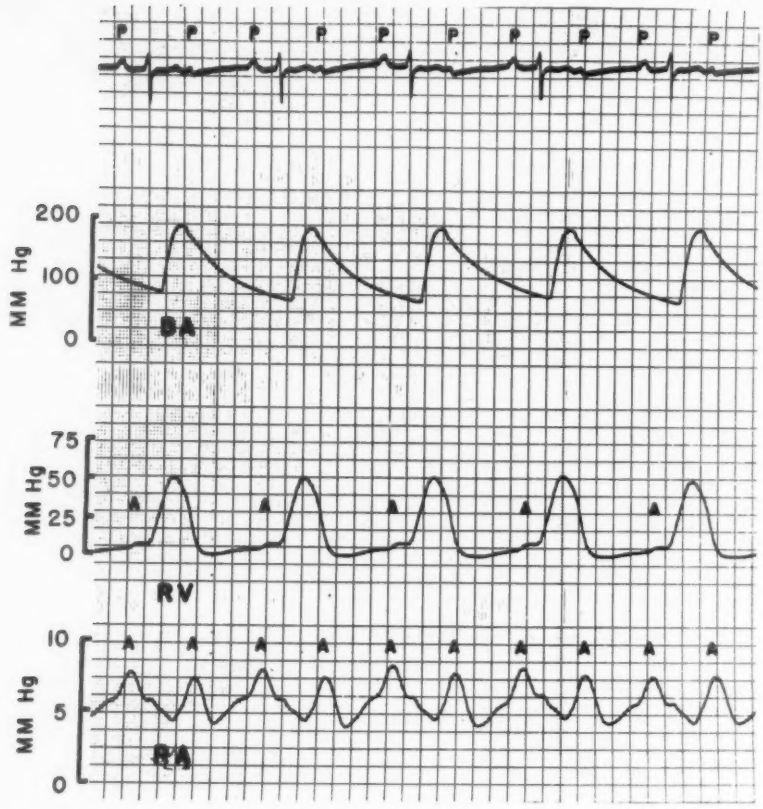


FIG. 1B. Case 6. Simultaneous electrocardiogram and pressure tracings from the brachial artery, right ventricle and right atrium. Right atrial pressure waves are present on the right ventricular pressure tracing, occurring from 0.06 to 0.12 second after their appearance in the right atrium.

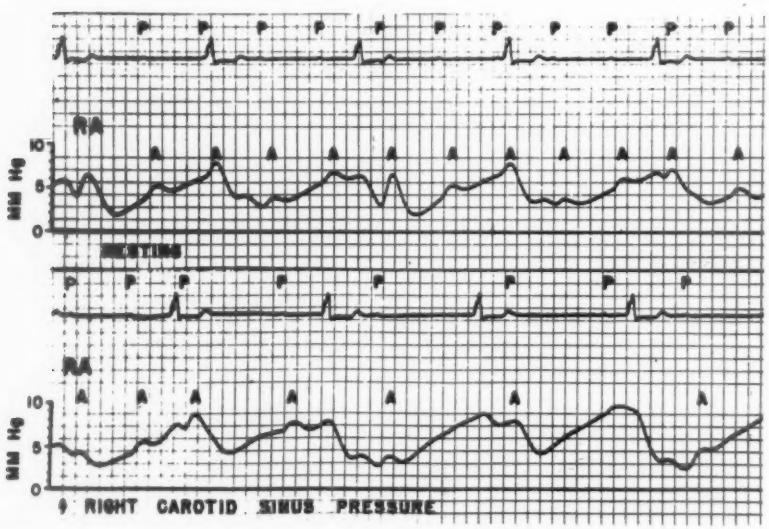


FIG. 2. Case 2. Right atrial pressure rises as ventricular diastole progresses. Carotid sinus pressure causes considerable atrial slowing. Atrial pressure rises higher with the slower atrial rate than with the more rapid atrial rate.

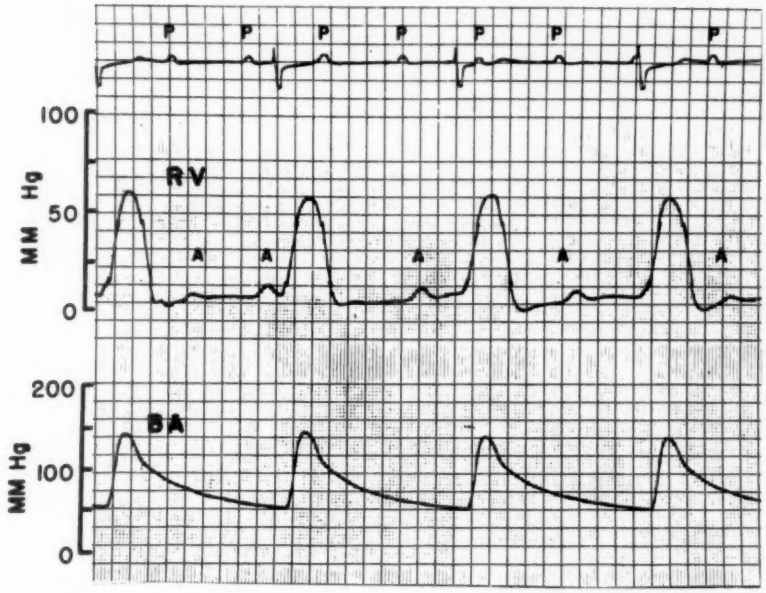


FIG. 3A. Case 4. Simultaneous electrocardiogram and pressure tracings from the right ventricle and brachial artery. Right atrial pressure waves are again noted on the ventricular pressure tracing, occurring from 0.12 to 0.18 second after the onset of the P waves.

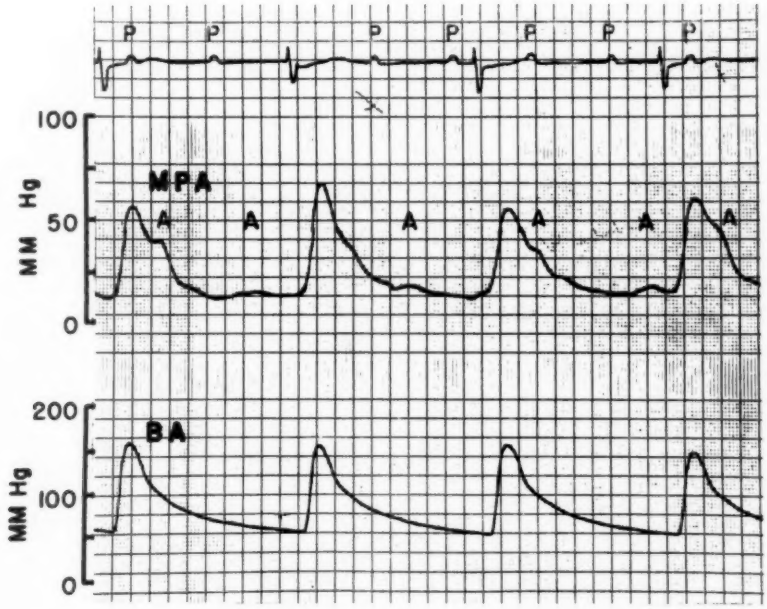


FIG. 3B. Case 4. Simultaneous electrocardiogram and pressure tracings from the main pulmonary artery and brachial artery. Atrial pressure waves are noted in the main pulmonary artery pressure tracing, occurring 0.20 second or later after the onset of the P waves.

TABLE I
Catheterization Findings in Six Cases of Heart Block

| Case No. | Rhythm | Rate | | Right Atrial Systolic/ Maximum Diastolic (mm. Hg) | Right Ventricular Systolic/ Maximum Diastolic (mm. Hg) | Main Pulmonary Artery (mm. Hg) | | Total Pulmonary Vascular Resistance (dynes sec. cm.$^{-5}$) | Brachial Artery (mm. Hg) | | | Total Systemic Vascular Resistance | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Atrial | Ventricular | | | Systolic/ Diastolic | Mean | | Systolic/ Diastolic | Mean | Normal[14] Mean | Dynes sec. cm.$^{-5}$ | Normal (dynes sec. cm.$^{-5}$) | Increase above Normal[14] (%) |
| 1 (P. C.) | Complete block | 68 | 26 | 4–12/5 | 85/8 | 75/12 | 24 | 835 | 200/60 | 72 | 90 | 2,505 | 1,830 | 39 |
| 2 (L. R.) | Complete block | 68 | 27 | 6–10/7 | 45/7 | 45/10 | .. | .. | 145/50 | .. | 90 | .. | .. | .. |
| 3 (P. P.) | Complete block | 86 | 28 | 8–12/8 | 60/8 | 54/9 | 22 | 765 | 182/61 | 82 | 91 | 2,852 | 1,690 | 70 |
| 4 (S. G.) | Complete block | 70 | 30 | 4–17/6 | 64/8 | 61/12 | 26 | 630 | 156/54 | 83 | 91 | 2,006 | 1,690 | 18 |
| 5 (H. R.) | 2:1 block | 68 | 34 | 4–6/4 | 42/5 | 42/8 | 20 | 842 | 140/60 | 73 | 97 | 3,072 | 1,680 | 83 |
| 6 (A. S.) | 2:1 block | 78 | 39 | 5–8/6 | 50/8 | 45/8 | 20 | 533 | 175/70 | 86 | 90 | 2,293 | 1,820 | 25 |

but was normal in one of the patients with 2:1 heart block.

### Comments on the Hemodynamic Findings

*Right Atrial Pressure:* Right atrial systolic peaks showed a wide range in patients with complete heart block, and in three of the four reached at least 12 mm. Hg. Atrial systolic pressures tended to be relatively high in late ventricular diastole as observed by Eldridge and Hultgren,[2] and were highest when atrial systole occurred at the time of atrioventricular valve closure, as noted by Coblenz et al.[3]

In one patient with 2:1 block the occurrence of atrial systole at the time of atrioventricular valve closure was not associated with unusually high *a* waves. In this instance premature ventricular contractions occurred relatively early following a normal beat (Fig. 1A, Case 6). Atrial systole occurring at the same time as ventricular systole (as documented by simultaneous pressure curves via a double-lumen catheter in the right ventricle and right atrium, in conjunction with the electrocardiogram) was not associated with unusually large *a* waves. This absence of large *a* waves at the time of simultaneous atrioventricular systoles may be attributable to the only partial diastolic filling which has occurred in the ventricle, or in the atrium, or in both ventricle and atrium at this time.

The right atrial diastolic pressure also tended to rise during the course of ventricular diastole, but this rise was modified or reversed by inspiration. With the slowing of atrial rate due to carotid sinus pressure, the diastolic pressure in the atrium rose even higher.

*Right Ventricular Pressure:* The systolic pressures in the right ventricle were elevated in all patients. The ventricular systolic peaks in individual patients varied somewhat from beat to beat, tending to be higher when the preceding end diastolic pressures were higher. The ventricular systolic peaks also tended to be higher when atrial systolic contractions of higher magnitude occurred shortly before closure of the atrioventricular valves. Abrahams and Wood[5] noted that conversion from a sinus to a nodal rhythm, in patients with pulmonic stenosis, was associated with a drop in right ventricular systolic pressure. They concluded that a strong right atrial contraction in presystole assisted the right ventricle in generating a high systolic pressure. The higher atrial systolic peaks

TABLE II
Further Catheterization Findings in Six Cases of Heart Block

| Case No. | Rhythm | Age (yr.) | Ventricular Rate | Oxygen Consumption (cc./min./M² BSA) | Arteriovenous Oxygen Difference (vol. %) | Cardiac Output (L./min.) | Cardiac Index (L./min./M² BSA) | Stroke Vol. (cc.) | Stroke Index | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | (cc./beat/M² BSA) | Normal[15] (cc./beat/M² BSA) | Increase above Normal[15] (%) |
| 1 (P. C.) | Complete block | 75 | 26 | 85 | 6.6 | 2.3 | 1.3 | 88 | 50 | 39 | 28 |
| 2 (L. R.) | Complete block | 76 | 27 | 96 | 4.3 | 2.9 | 2.3 | 107 | 85 | 39 | 118 |
| 3 (P. P.) | Complete block | 63 | 28 | 89 | 6.1 | 2.3 | 1.4 | 82 | 50 | 41 | 22 |
| 4 (S. G.) | Complete block | 69 | 30 | 96 | 4.8 | 3.3 | 2.0 | 110 | 67 | 41 | 63 |
| 5 (H. R.) | 2:1 block | 52 | 34 | 95 | 6.8 | 1.9 | 1.4 | 56 | 41 | 41 | 0 |
| 6 (A. S.) | 2:1 block | 74 | 39 | 82 | 4.4 | 3.0 | 1.8 | 76 | 46 | 39 | 18 |

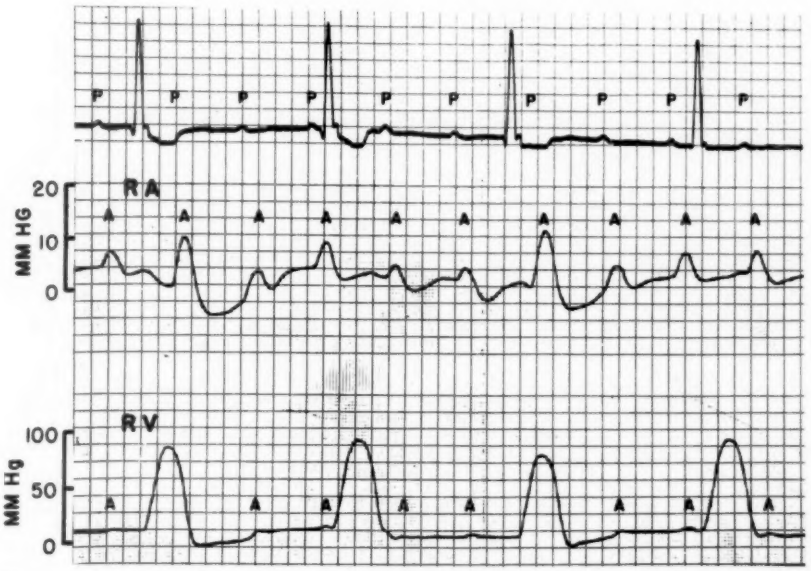


FIG. 4. Case 1. Simultaneous electrocardiogram and pressure tracings from the right atrium and right ventricle. Atrial pressure waves appear on the right ventricular pressure tracing 0.07 to 0.11 second after their appearance in the right atrium.

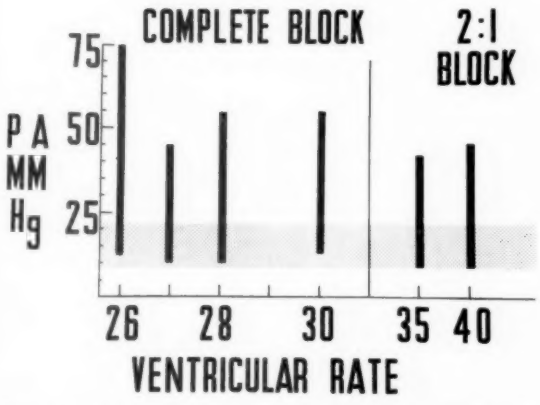


FIG. 5A. The pulmonary artery pressures are shown in relation to ventricular rates. The systolic pressures all are elevated while the diastolic pressures are normal. Dotted area shows normal pressure zone.

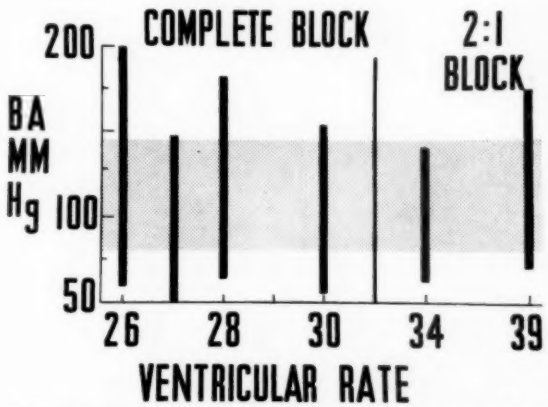


FIG. 5B. The brachial artery pressures are shown in relation to ventricular rates. Brachial artery pulse pressures all are increased.

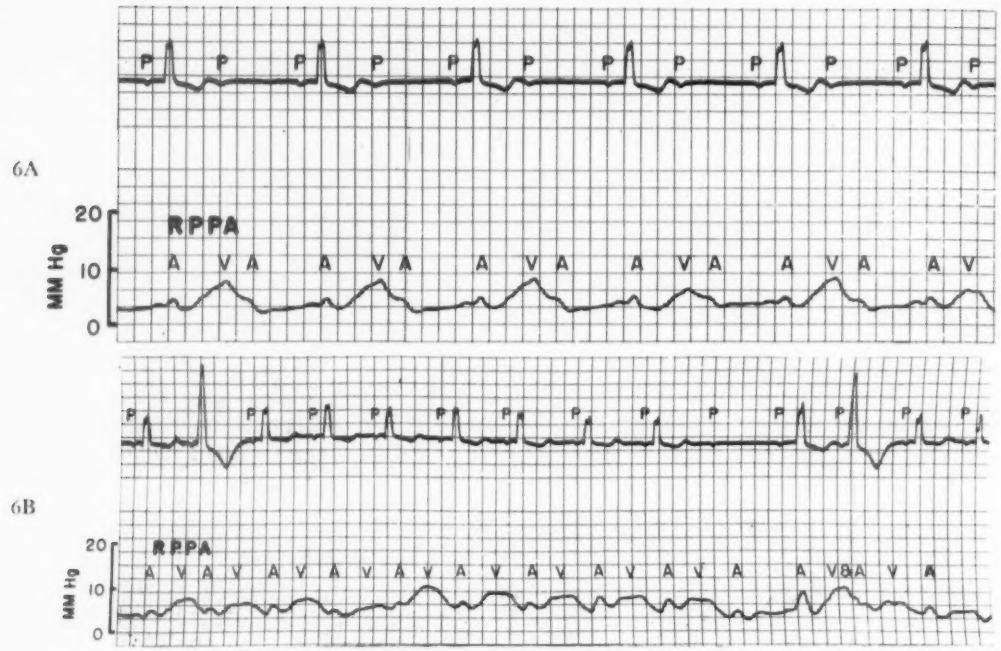


FIG. 6A. Case 5. Simultaneous electrocardiogram and wedged pulmonary artery pressure tracings. A 2:1 atrioventricular block is present. The wedged tracing shows an *a*, *a*, *v* pressure wave pattern.

FIG. 6B. Case 5. Conversion to sinus rhythm doubling the ventricular rate. The wedged pulmonary artery tracing now shows an *a*, *v*, *a*, *v* pressure wave pattern.

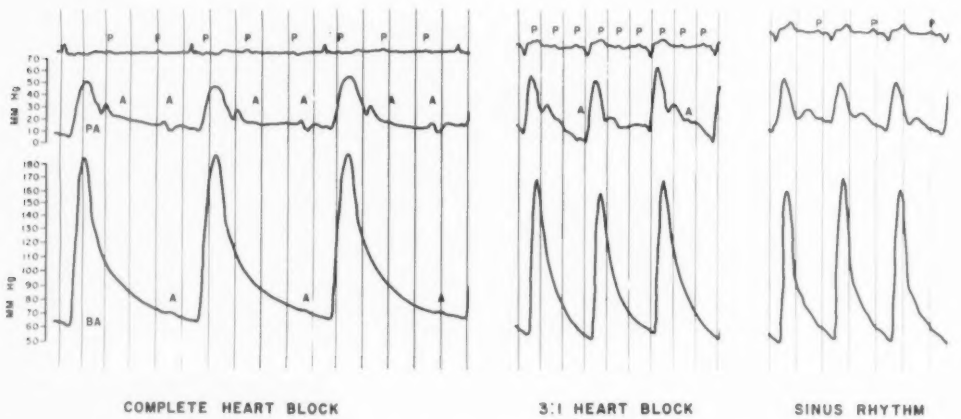


FIG. 7. Case 3. Simultaneous electrocardiogram and pressure tracings from the pulmonary and brachial arteries. The record is divided into three sections. Prior to injection of Isuprel complete heart block is present (record on left). Atrial pressure deflections are noted on both the pulmonary and brachial artery pressure tracings. Following injection of Isuprel, 3:1 atrioventricular block develops initially (middle record). Subsequently sinus rhythm occurs (record on right).

in the current study, however, occurred in relation to the higher ventricular diastolic pressures. In many instances atrial systoles did not occur in late diastole and yet subsequent ventricular beats showed high systolic peaks. These high ventricular systolic peaks in the absence of preceding large atrial systolic waves were related to the magnitude of the ventricular diastolic pressure.

The end diastolic pressures did not indicate right ventricular failure in any instance.

Atrial systolic pressure waves appeared in

the right ventricular pressure tracings from 0.06 to 0.12 second after their onset in the atrium.

*Pulmonary Artery:* The pulmonary artery systolic pressures were increased and the diastolic pressures were normal or subnormal for the age group. Mean pulmonary artery pressures all were elevated.

Atrial systolic pressure waves were visible on the pressure curve of the main pulmonary artery in systole and diastole. In Case 4 these atrial systolic waves appeared on the pulmonary artery pressure curve 0.20 second or more, in most instances, after the onset of the P wave (Fig. 3B). In the same case the onset of the atrial systolic pressure waves in the right ventricle occurred most frequently from 0.12 to 0.18 second after the onset of the P wave. These pressure tracings from the main pulmonary artery and right ventricle were not taken simultaneously. However, the earlier occurrence of the atrial deflection in the ventricle than in the pulmonary artery warrants the opinion that the wave in the pulmonary artery is being transmitted via the right ventricle. This is in contrast to the findings of Donoso, Braunwald, Jick and Grishman,[4] who noted these atrial waves earlier in the pulmonary artery than in the right ventricle. They noted the contour of the waves in the pulmonary artery which were associated with atrial contraction to be irregular in appearance, presumably similar to what might be expected from the vibrations resulting from the external impact of the atrium on the pulmonary artery. In Case 4, however, the atrial deflections in the main pulmonary artery were not of this type, but similar to those found in the right ventricle. It is our opinion that in this patient these atrial waves in the pulmonary artery were transmitted via the right ventricle.

*Brachial Artery:* Brachial artery systolic pressures were 175 mm. Hg or more in three of the six patients (Fig. 5B). Mean brachial artery pressures were low in all patients for the age group concerned, averaging 79 mm. Hg. This is in keeping with the observation by Penton, Miller and Levine[6] that hypertension, although often associated with acquired complete heart block, is not a necessary feature of it. Pertinent, too, are the findings of Campbell and Thorne,[7] who, in following up seven patients with congenital complete heart block for twenty-five years, found that the blood pressure showed no tendency to rise with the passage of time. The low mean brachial artery pressures were in contrast to the mean pulmonary artery pressures which were elevated.

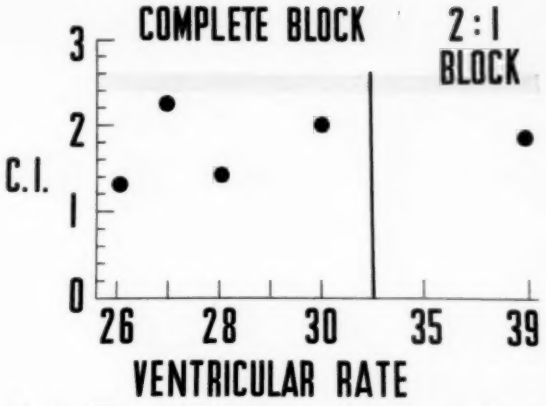


FIG. 8. The cardiac indices are shown in relation to the ventricular rates. Indices range from 1.3 to 2.3 L./min./M² BSA. Normal cardiac indices for people of this age group are shown by the dotted lines.

*Cardiac Output and Stroke Volume:* All the patients had diminished cardiac outputs. This is in contrast to congenital complete heart block without accompanying defects, when cardiac outputs may be normal.[8] The decreased cardiac output was in part compensated for by increased oxygen extraction, as evidenced by increased arteriovenous oxygen differences, in three of the six patients (Table II). Despite this, however, the oxygen consumption was reduced in all instances (Table II). Since there was no other evidence of hypothyroidism in any of these patients, the low oxygen consumption suggests an adaption to the low cardiac output.

The slow ventricular rates were partly offset also by the prolonged ventricular diastolic filling periods and increased stroke volumes which occurred in five of the six patients. In no instance, however, was the increase in stroke volume sufficient to result in normal cardiac output.

The inability to increase stroke index above 28 per cent of normal in four of the six patients is noteworthy. The normal heart may be capable of increasing resting stroke volume up to two and a half times.[9] In all these patients, however, coronary artery disease was present in addition to heart block. Coronary artery disease has been implicated as the most common cause of acquired complete heart block.[6,10] Presumably, the heart was limited in its ability to increase stroke volume by the abnormal myocardium.[11]

TABLE III

Effect of Injection of Isuprel into Right Ventricle in Two Cases of Heart Block

| Time of Study | Rate | | Rhythm | Oxygen Content | | | Right Ventricle (mm. Hg) | Main Pulmonary Artery | | Total Pulmonary Vascular Resistance (dynes sec. cm.$^{-5}$) | Brachial Artery | | Total Systemic Vascular Resistance (dynes sec. cm.$^{-5}$) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Atrial | Ventricular | | Pulmonary Artery (vol. %) | Brachial Artery (% saturation) | Brachial Artery (vol. %) | | (mm. Hg) | Mean (mm. Hg) | | (mm. Hg) | Mean (mm. Hg) | |
| Case 3 | | | | | | | | | | | | | |
| Before Isuprel... | 86 | 28 | Complete block | 9.2 | 56 | 15.3 | 60/7 | 54/9 | 22 | 765 | 182/61 | 82 | 2,852 |
| After Isuprel | | | | | | | | | | | | | |
| 30 sec..... | 150 | 50 | 3:1 block | 11.5 | 70 | 15.3 | 60/1 | 54/5 | 18 | 351 | 164/56 | 80 | 1,561 |
| 17 min..... | 70 | 70 | Sinus rhythm | 12.5 | 77 | 15.5 | 62/0 | 52/9 | 18 | 272 | 165/53 | 90 | 1,359 |
| Case 4 | | | | | | | | | | | | | |
| Before Isuprel... | 80 | 30 | Complete block | 11.6 | 65 | 16.3 | 64/3 | 61/12 | 26 | 630 | 156/54 | 83 | 2,006 |
| After Isuprel | | | | | | | | | | | | | |
| 1 min..... | * | 80 | Complete block | .. | .. | .. | .. | 37/13 | 23 | .. | 120/45 | 70 | ... |
| 2 min..... | 120 | 64 | Complete block | .. | .. | .. | .. | 45/12 | 24 | .. | 145/52 | 75 | ... |
| 3 min..... | 120 | 50 | Complete block | .. | .. | .. | .. | 75/17 | 35 | .. | 128/58 | 80 | ... |
| 6 min..... | 108 | 50 | Complete block | 14.1 | 79 | 16.6 | .. | 65/13 | 31 | 443 | 123/67 | 77 | 1,100 |

* Indeterminate.

*Vascular Resistances:* Despite the low cardiac outputs, these patients were able to maintain mean pressures in the pulmonary artery which were somewhat elevated (Table I). The total pulmonary vascular resistance, therefore, was elevated considerably.

The mean pressures in the brachial artery were subnormal; however, the total systemic vascular resistances were increased (Table I). This increase in systemic vascular resistance was possible since the decrease in mean brachial artery pressures was less proportionately than the decrease in cardiac outputs.

The increased vascular resistances in the presence of lowered cardiac outputs indicated either considerable compensatory ability on the part of both the pulmonic and systemic circulations, or changes in resistance secondary to systemic and pulmonic vascular disease. The changes which occurred with isoproterenol clarified this last possibility in the cases concerned.

### Hemodynamic Effects of Isoproterenol

*Isoproterenol:* Isuprel in a dose of 0.15 mg. was injected through the catheter into the pulmonary artery in two patients with complete heart block (Cases 3 and 4). In these two patients the amount of Isuprel which was given was predetermined by testing with various dosages of the drug the day before cardiac catheterization. Neither patient had bronchial asthma. In one, the rhythm changed from complete heart block to a 3:1 block and then to a sinus rhythm (Fig. 7, Case 3 and Table III). In the other, the rhythm remained unchanged but both atria and ventricles accelerated.

In Case 3 of the present study, injection of Isuprel was followed in thirty seconds by an increase in atrial rate from 86 to 150 and in ventricular rate from 28 to 50 per minute, with the rhythm converting from a complete to a 3:1 A-V block (Fig. 7, Case 3 and Table III). With this increase in ventricular rate, the cardiac output rose from 2.3 L./min. to 4.1 L./min. (Table IV). This occurred without a change in stroke volume, which remained constant at 82 cc. per beat. The increase in cardiac output thus was the result of the increase in heart rate. The increase in cardiac output was accompanied by a fall in arterio-

TABLE IV
Further Effects of Isuprel in Two Cases of Heart Block

| Time of Study | Oxygen Consumption (cc./min.) | Oxygen Consumption (cc./min./M² BSA) | Arteriovenous Oxygen Difference | Stroke Volume (cc.) | Cardiac Output (L./min.) | Cardiac Index (L./min./M² BSA) |
|---|---|---|---|---|---|---|
| Case 3 | | | | | | |
| Before Isuprel | 142 | 89 | 6.1 | 82 | 2.3 | 1.4 |
| After Isuprel | | | | | | |
| 30 sec | 158 | 99 | 3.8 | 82 | 4.1 | 2.5 |
| 17 min | 160 | 100 | 3.0 | 75 | 5.3 | 3.2 |
| Case 4 | | | | | | |
| Before Isuprel | 153 | 96 | 4.8 | 110 | 3.3 | 2.0 |
| After Isuprel | | | | | | |
| 1 min | .. | .. | .. | .. | .. | .. |
| 2 min | .. | .. | .. | .. | .. | .. |
| 3 min | .. | .. | .. | .. | .. | .. |
| 6 min | 140 | 88 | 2.5 | 112 | 5.6 | 3.4 |

venous oxygen difference from 6.1 to 3.8 vol. per cent due to an increase in the pulmonary artery oxygen content (Table IV).

The increase in cardiac output was associated with a small decrease in total pulmonary artery mean pressure and a marked decrease in total pulmonary vascular resistance (Table III). Brachial artery mean pressure was minimally lowered with the increase in cardiac output, but total systemic vascular resistance decreased markedly.

Seventeen minutes after the injection of Isuprel, the 3:1 block had been replaced by a sinus rhythm. The ventricular rate increased further from 50 to 70 per minute and cardiac output from 4.1 to 5.3 L./min. The arteriovenous oxygen difference decreased further from 3.8 to 3.0 vol. per cent due to an increase in the pulmonary artery oxygen content. This increase in cardiac output was associated with a decrease in stroke volume from 82 to 75 cc. per beat (Table IV). The increased cardiac output thus again was the result of the increase in heart rate. Although the brachial artery mean pressure rose from 80 to 90 mm. Hg, the total systemic vascular resistance decreased further, as did the total pulmonary vascular resistance.

In the other patient (Case 4) in whom Isuprel was injected through the catheter into the pulmonary artery, the rhythm did not change from complete heart block, but both atria and ventricles accelerated. The atrial rate increased from 80 per minute prior to injection of Isuprel to 120 per minute two minutes after the injection and at six minutes was 108 per minute. The ventricular rate increased from 30 to 80 per minute one minute after administration of Isuprel, then gradually fell to 50 per minute.

The increase in ventricular rate was associated with an increase in cardiac output from 3.3 to 5.6 L./min. and with a fall in arteriovenous oxygen difference. The increase in cardiac output occurred without a change in stroke volume (110 to 112 cc. per beat). The increase in cardiac output thus again was a result of the increase in heart rate.

The sudden increase in ventricular rate from 30 to 80 per minute was accompanied by a fall in pulmonary and systemic mean arterial pressure. This period was characterized by multifocal ventricular beats. As the multifocal ventricular beats diminished and the ventricular rate slowed from 80 to 50 per minute, the pulmonary and systemic mean arterial pressures rose. The pulmonary artery mean pressure continued to rise and, six minutes after administration of Isuprel, was higher than the mean pressure before the drug was given. Despite this, the total pulmonary vascular resistance diminished considerably, as did the total systemic vascular resistance.

*Comments on the Effects of Isuprel:* In a recent study Stack et al.[11] reported on the hemodynamic changes with Isuprel in five patients with complete heart block. They noted that

Isuprel led to ventricular acceleration and increased cardiac output, with a change toward normal in cardiac dynamics. In all their patients complete heart block persisted following administration of Isuprel.

In Cases 3 and 4 in the present study injection of Isuprel was also followed immediately by acceleration of the ventricular rate and increase in cardiac output. This was achieved without an increase in stroke volume. The primary cardiac effect of Isuprel in these patients would appear to have resulted from the accelerated discharge of idioventricular foci.[11]

The changes which occurred with Isuprel were similar in Cases 3 and 4, despite the fact that the rhythm converted from complete heart block to sinus rhythm in Case 3, but persisted as complete heart block in Case 4. The common denominator in these patients was the acceleration of the ventricular rate and not the change in rhythm. The maintenance of an essentially unaltered stroke volume, in the presence of a much more rapid ventricular rate, offers indirect evidence for an associated stimulatory effect of Isuprel on the ventricular muscle.[12]

The increase in cardiac output with Isuprel was associated with a marked fall in both pulmonary and systemic vascular resistance. Since Isuprel produces peripheral vasodilatation and lowering of blood pressure,[13] the fall in vascular resistance may be attributed to the direct effect of Isuprel on the pulmonary and systemic vasculature. The possibility remains, however, that increased cardiac output, *per se*, may also be an important factor in influencing the drop in vascular resistance by reversing the compensatory constriction of the vasculature which had resulted from the low cardiac output.

Despite considerable increases in cardiac output after administration of Isuprel, oxygen consumption was only slightly altered. The pulmonary artery oxygen saturations rose to high levels (77 per cent in Case 3 and 79 per cent in Case 4). These high pulmonary artery oxygen saturations were possible since the oxygen consumption indices continued to be low (100 cc./min./$M^2$ in Case 3 and 88 cc./min./$M^2$ in Case 4). The persistence of these low oxygen consumption indices, in the presence of normal cardiac outputs, tends to confirm the impression that these indices reflect a long term metabolic adjustment to the diminished cardiac outputs.


## Summary

Six patients with acquired heart block and ventricular rates below 40 per minute were catheterized. Pertinent hemodynamic findings were: (1) elevated right atrial and right ventricular systolic pressure; (2) atrial systolic waves transmitted to both the right ventricle and main pulmonary artery successively; (3) giant atrial *a* waves occurring at the time of simultaneous atrioventricular systoles, but not when this occurred in or near early diastole of the preceding ventricular beat; (4) systolic pulmonary hypertension; (5) reduced mean brachial artery pressure, but elevated mean pulmonary artery pressure; (6) increased total vascular resistance of both the pulmonic and systemic circulations; (7) reduced oxygen consumption; (8) reduced cardiac index; and (9) increase of stroke index to 28 per cent or less above normal in four of the six patients.

The injection of Isuprel via a catheter directly into the main pulmonary artery in two patients resulted in: (1) more rapid ventricular rate; (2) conversion to a sinus rhythm in one; (3) unaltered stroke volume; (4) increased cardiac output; (5) unaltered oxygen consumption; (6) decreased arteriovenous oxygen difference; and (7) decreased total vascular resistance in both the pulmonic and systemic circulations.



## Acknowledgement

We wish to express thanks to John and Fanny Hertz for financial aid and encouragement in this study.


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# Some Unusual Manifestations of Cerebral Aneurysms*

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INTELLIGENT management of intracranial hemorrhage depends on early diagnosis and localization of the origin of bleeding. This cannot always be achieved on a clinical basis. A lumbar puncture and arteriography must be performed in every case. In recent years we have learned that the most common cause of spontaneous or non-traumatic intracranial hemorrhage has been ruptured aneurysms. In addition to symptoms of diffuse cerebral dysfunction and meningeal irritation caused by the subarachnoid hemorrhage, an aneurysm may produce focal symptoms either by compression without hemorrhage or by focal intracerebral bleeding.

Focal symptoms caused by expanding aneurysms are usually localized to the base of the brain. Thus, the sudden or rapid appearance of a unilateral ophthalmoplegia in a patient who has severe headache and mental confusion suggests the possibility of a leaking aneurysm within the circle of Willis. In such a case a lumbar puncture and an arteriogram would be performed to establish the nature and precise location of the arterial defect. On the other hand, the manifestations of aneurysms in certain cases, particularly when there is no bleeding, may be so unusual or the clinical background may be so colored that another cause for the symptoms is erroneously suspected. In these cases, arteriography may thus not be performed, or if performed may be incomplete, so that the investigation stops with the finding of one normal carotid artery system, the vertebral arteries and the other carotid not being explored.

These considerations were particularly impressive to us when we encountered a series of patients recently whose symptoms were subsequently proved to be caused by aneurysms, but in whom the diagnosis was not considered strongly at first or was arrived at only with difficulty. The unusual features and diagnostic difficulties in six of this series of cases will be described and discussed.

## CASE REPORTS

CASE 1. *Hypertension; Congestive Failure; Psychosis; Dicumarol:* A sixty-five year old physician was admitted to the hospital in a coma and with severe pulmonary edema. His congestive failure and pulmonary symptoms responded to vigorous therapy and he was given dicumarol for suspected myocardial infarction. Concomitantly he became more alert. There was no history of hypertension. The blood pressure on admission was 260/120 mm. Hg and returned to normal after a few days.

On the fifth day he became hostile, delusional, uncooperative and aggressive. Mental status could not be examined in detail but no clear stigmata of brain disease were elicited. Retinal hemorrhages and exudates were seen in both fundi. There were no meningeal or focal neurologic signs. Lumbar puncture revealed uniformly bloody fluid, the supernatant of which was deeply xanthochromic. Administration of dicumarol was then stopped. X-ray films of the skull were normal, a calcified pineal body being present in the usual position. The patient improved temporarily. He was less irritable and became more cooperative. However, on the tenth hospital day he suddenly became comatose with loss of corneal and pupillary light reflexes. A lumbar puncture was performed at once and revealed clear, colorless fluid. Later, while the spinal needle was in place, the fluid became first blood-tinged and then increasingly bloody. Four days thereafter a right carotid arteriogram was performed which revealed a normal vascular tree. Contralateral filling could not be obtained. The patient died on the twenty-first hospital day.

*Autopsy* revealed several old coronary occlusions and a markedly hypertrophic heart weighing 820 gm. The brain showed a ruptured aneurysm in the region

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of the anterior communicating artery which appeared to arise from the junction of that artery with the left anterior cerebral artery. There was considerable hemorrhagic destruction of the frontal lobes with hemorrhage extending through the genu of the corpus callosum into the third ventricle and both lateral ventricles.

*Comment:* This patient exhibited a constellation of signs and symptoms that tended to obscure the true diagnosis in the few days prior to his relapse into a coma. The earlier symptoms of an acute change in behavior were without signs of organicity. However, the onset of a first psychotic episode so late in life suggested organic disease. It seemed reasonable in a person with evidence of severe vascular disease that both the mental symptoms and coma were manifestations of cerebral circulatory insufficiency, particularly in the absence of meningeal signs. Furthermore, even after he became comatose and a spinal tap was performed, the prothrombin level was sufficiently prolonged that the bleeding could have been attributed to the bleeding tendency. Finally, incomplete arteriographic studies failed to reveal the aneurysm.

CASE 2. *History of Headache and Coma; Progressive Dystaxia and Aphasia; Right Focal Seizures; Left Optic Neuropathy:* A sixty-six year old man was admitted to the hospital because of inability to speak for two weeks. Eight years before admission he had had sudden onset of headache followed by coma. There was recovery but "memory" remained poor and he was no longer able to function productively. For two or three years prior to admission he exhibited progressive difficulty in walking and fell frequently. Speech also became worse and for several weeks he had been unable to express himself verbally. Several episodes of "shakings" or twitchings of the right hand were noted by his family. When examined he appeared alert and was able to imitate gestures. However, he was aphasic and no verbal contact could be made.

The left eye was amaurotic and the left optic disc was pale. The left pupil responded to light consensually but not directly, the right responding to direct stimulation but not consensually. There was a right lower mimetic-type facial weakness. The gait was broad-based and unsteady with short, shuffling steps. On testing for Romberg's sign, he fell backward. No weakness or incoordination was noted in the extremities. The deep tendon reflexes were more active on the right and a Babinski sign was present on the right. Sensation appeared to be intact.

The spinal fluid, under normal pressure, was clear and colorless and contained a total protein of 94 mg. per cent. X-ray films of the skull revealed a thin, irregular, sickle-like calcification just to the left of the anterior clinoids. Left carotid arteriography revealed a large aneurysm at the bifurcation of the internal carotid artery, having an appearance much like a large subfrontal mass (Fig. 1). The patient was discharged without further change in his condition. It was reported that he died one year later but no autopsy was performed.

FIG. 1. Case 2. Left carotid arteriogram (anteroposterior view). A partially filled aneurysm of the left anterior cerebral artery is seen. The aneurysm elevates both anterior cerebral arteries, left more than right, and deviates them to the right.

*Comment:* The unusual feature in this case is the two different modes of presentation, separated by an interval of eight years. The initial episode eight years prior to admission probably represents a subarachnoid hemorrhage even though the diagnosis was not established at that time. (No lumbar puncture had been performed.) The recent symptoms were suggestive of a progressive subfrontal mass lesion mimicking a meningioma of the left anterior fossa.

CASE 3. *Hypertensive Cardiovascular and Renal Disease; Right Hemiparesis; Left-sided Findings; Meningeal Signs with Acellular Spinal Fluid:* A thirty-nine year old woman was admitted to the Neurology Service because of two days of right-sided weakness. There was a ten-year history of marked hypertension, albuminuria and episodes of bifrontal headache accompanied by blurred vision. Two days before

FIG. 2A. Case 3. Right vertebral arteriogram (lateral view). An aneurysm of the rostral end of the basilar artery is demonstrated.

FIG. 2B. Case 3. Right vertebral arteriogram (anteroposterior view). The aneurysm involves the origins of the superior cerebellar and posterior cerebral arteries on both sides.

admission the patient awoke with weakness and loss of sensation in the right arm. The following day weakness of the right leg was noted.

Examination revealed a blood pressure of 230/150 mm. Hg and an enlarged heart with a basilar systolic murmur. There was a right homonymous hemianopia for form and color. A flaccid right hemiparesis was noted, with more marked involvement of the upper extremity. Vibration was lost over the sacrum. The patient had a mildly stiff neck and a positive Lasègue sign on the right. Lumbar punctures on two occasions revealed clear, colorless fluid under normal pressures. The fluid contained no cells and the total protein was 83 and 85 mg. per cent. The visual defect cleared the day following admission and the right hemiparesis slowly improved. However, the patient began making errors in proprioception on the left and a definite left Babinski sign appeared. Bilateral sacral and iliac crest defects in vibration persisted.

Left carotid arteriography showed elevation of the middle cerebral group of vessels. A right vertebral arteriogram revealed a large aneurysm of the rostral end of the basilar artery at the junction of both posterior cerebral arteries and both superior cerebellar arteries (Fig. 2). The patient was discharged from the hospital and has not been seen subsequently.

*Comment:* The bilaterality of this patient's findings suggested multiple foci of disease, and with the background of severe arterial hypertension there was little reason to doubt that arteriolar disease was the cause. It was believed that the bilaterality of signs demanded further exploration. Although the elevation of the left middle cerebral artery in the carotid angiogram might have accounted for the right-sided symptoms, it did not explain impairment of position sense in the ipsilateral left foot, the bilateral vibration sense defects and the bilateral Babinski signs. Consequently, a vertebral angiogram was performed and only this procedure showed the true nature of the disorder, namely, aneurysm. It is of interest that the patient had meningeal signs even though there were no cells in the spinal fluid. The elevation of the left middle cerebral artery probably represented bleeding into or beneath the left temporal lobe.

CASE 4. *Hypertension; Personality Change; Aphasia:* A fifty-seven year old woman was admitted to the hospital with speech difficulty of ten hours' duration. Six days before admission there had been an episode of sudden and severe head and neck pain. Later that day she appeared elated and during the following days appeared to work harder than usual. On the day of admission she suddenly lost the ability to speak. Blood pressure was 180/100 mm. Hg. There was a distinct aphasia, mostly expressive. Minimal right hyperreflexia was found and there was a sensory deficit in the right hand to double simultaneous stimulation. No meningeal signs were elicited. Lumbar puncture showed grossly bloody spinal fluid.

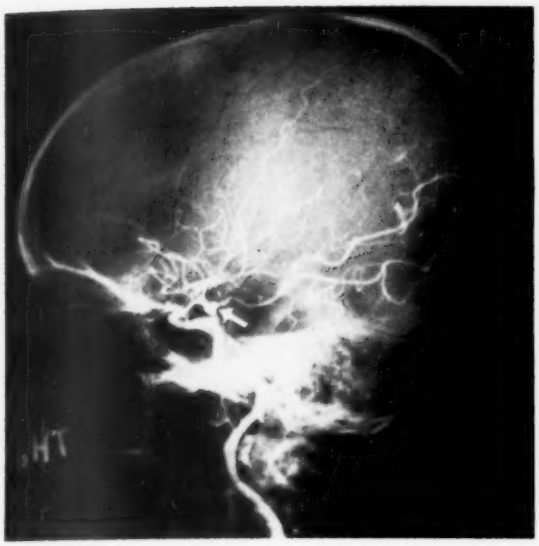

FIG. 3. Case 5. Right carotid arteriogram (lateral view). An aneurysm is seen at the junction of the right internal carotid and posterior communicating arteries. The internal carotid artery just proximal to the siphon is narrowed, presumably because of spasm.

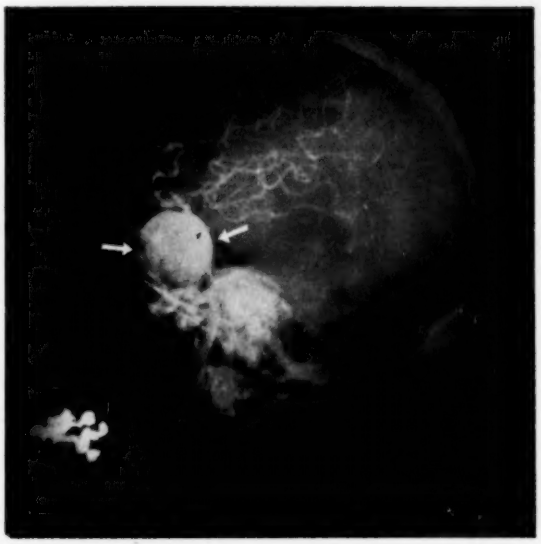

FIG. 4. Case 6. Left carotid arteriogram (lateral view). A giant aneurysm is seen originating on the infraclinoid portion of the left internal carotid artery.

Left carotid arteriography was interpreted as normal.

Five days later the patient had a fresh episode of subarachnoid bleeding with a grand mal seizure, increase in aphasia and more prominent right-sided findings. Twelve days after admission she awoke with complete palsy of the left third nerve. A second left carotid arteriogram then revealed a saccular aneurysm at the junction of the internal carotid and posterior communicating arteries. Her course was progressively downhill with seizures, and she died twenty-eight days after admission.

*Autopsy* confirmed the presence of a subarachnoid hemorrhage from a ruptured aneurysm at the left posterior communicating-internal carotid junction. The hemorrhage had ruptured into the left temporal lobe and left lateral ventricle.

*Comment:* This patient presented with aphasia and no meningeal signs. If it were not for a spinal tap, the diagnosis of subarachnoid bleeding would not have been established early in the course. The sudden pain six days before admission probably represented the initial episode of bleeding and the personality changes may also be related. The initial left carotid angiogram was thought to be normal and since the patient's hypertension seemed to be sufficient basis for intracranial bleeding, no further tests appeared necessary. However, the constellation of symptoms that developed under observation strongly suggested an aneurysm in the region of the left posterior communicating artery. A second arteriogram did indeed demonstrate such an aneurysm. At this point, re-examination of the initial arteriographic study showed that the aneurysm was present but was to a large extent fortuitously obscured by the carotid siphon and the base of the skull. A few degrees of rotation in any of the arteriographic views would have made the aneurysm obvious.

CASE 5. *Multiple System Disease with Vasculitis; Psychosis Followed by Coma:* A forty-nine year old woman was admitted to the Medical Service because of acute onset of fever, myalgias, arthralgias and skin lesions on both legs. The skin lesions were biopsied and the pathologist interpreted the slides as representing a vasculitis. Ten days after the onset she awoke during the night and was found to be agitated and hallucinating. The hallucinations were mostly religious in content and appeared to be both auditory and visual. A barbiturate was administered and the patient slept. The following morning she was lethargic and obtunded. Nuchal rigidity was now elicited.

Lumbar puncture yielded a slightly bloody fluid without xanthochromia. This was thought to be due to trauma at lumbar puncture. Hence the tap was repeated a few hours later with the same results. She became confused and disoriented and showed downward drift of the left upper extremity. Later, retinal hemorrhages, left hemiparesis and left hemisensory findings were noted. The left-sided symptoms became worse and the patient was soon stuporous.

Right carotid arteriography revealed an aneurysm

in the region of the junction of the posterior communicating artery and the internal carotid artery (Fig. 3). Left carotid arteriography was normal. The patient died two days later.

*Autopsy* confirmed the presence of subarachnoid hemorrhage and a ruptured aneurysm in the location predicted by the x-ray studies. There was bleeding into the right temporal lobe and the brain stem was studded with small hemorrhages. The cerebral vessels and the aneurysm were not involved by the vasculitis noted in the skin biopsy.

*Comment:* This patient exhibited an acute psychosis that was not clearly related to structural brain disease. The presence of a diffuse vasculitis was invoked as a possible cause of the patient's symptoms. Furthermore, the lumbar punctures were not conclusive and were thought to be traumatic. These factors all tended to obscure the correct diagnosis.

Case 6. *Exotropia; Facial Pain:* A fifty year old woman was admitted with an eighteen-month history of left facial pain. Twenty years before admission she noted difficulty in reading and was treated for exotropia of the left eye. Diplopia ensued ten years later. The diplopia persisted and became more noticeable. Eighteen months before admission she noted episodes of sharp, throbbing pain in the left upper lip and in the gum in this region. There was also a continuous mild pain in the left side of the face. Two months before admission the patient experienced pressure on the left side of the nose. She then began to have three episodes a day of severe pain lasting thirty seconds. These attacks would begin in the left forehead, spread to the left eye, left side of the nose, cheek, lip and jaw and then into the left ear.

Examination revealed marked limitation of left eye movements in adduction and convergence and less on abduction. The left pupil was larger than the right but reacted normally. There was horizontal diplopia on all gaze movements to the left. No other findings were elicited. Spinal fluid examination was normal. X-ray films of the skull showed thinning of the floor of the left middle fossa with irregular erosion of the base in the region of the left foramina ovale and spinosum approximately 2.5 cm. in diameter.

Left carotid arteriography revealed a large aneurysm at the level of the carotid siphon and extending laterally approximately 2 cm. in diameter (Fig. 4). Right carotid arteriography revealed a similarly located aneurysm on the right, only 1 cm. in diameter. The patient was discharged without further therapy.

*Comment:* This patient had facial pain without sensory findings as her major symptom. The long-standing ophthalmoplegia involving first the oculomotor and then the abducens nerve was considered to be "ocular" in origin. Although a pathologic disorder at the base was considered, aneurysm of twenty years' duration did not seem likely. She also exhibited multiple aneurysms.

## Comments

The six patients with aneurysm described all presented with unusual diagnostic features during their course. There were other similar examples (not described herein). Unusual symptomatology or misleading background circumstances were responsible for the diagnostic difficulties in each case. The possibility of a cerebral aneurysm is so great in all cases of spontaneous subarachnoid bleeding that one must develop an obtuseness to apparently significant factors in the case that might militate against this diagnosis. Not until arteriography has adequately ruled out the presence of an aneurysm should other etiologic possibilities be invoked. This is readily apparent in a recently reported case[1] of active thrombocytopenic purpura with subarachnoid hemorrhage in which arteriography demonstrated an aneurysm.

*Associated Cardiovascular Conditions:* Cardiovascular conditions of one variety or another were present in four of the cases (Cases 1, 3, 4 and 5). These vascular disorders were in each case thought to be possible causes of the cerebral condition. Hypertension was the most frequent misleading symptom (Cases 1, 3 and 4). Although cerebral bleeding without the presence of an aneurysm is more common in persons with known hypertension, even in this group aneurysms are more frequently the source of bleeding than not.[2]

In two patients (Cases 3 and 5) there was clinical evidence of vasculitis which might have been held accountable for the cerebral symptoms. In Case 5 microscopic sections of the aneurysm showed no evidence of involvement by the inflammatory process. Hence, there was apparently no direct relationship between the rupture of this patient's aneurysm and the concomitant vasculitis.

One patient (Case 1) suffered from acute pulmonary edema with concurrent coma. When he became psychotic this personality change was initially thought to be a further manifestation of cerebral circulatory insufficiency secondary to his congestive heart failure. When blood was discovered in the subarachnoid space, the clotting defect due to dicumarol was thought to be responsible. In both instances the reasoning was not illogical, but nonetheless incorrect.

*Spinal Fluid Findings:* The absence of meningeal signs noted in Cases 1 and 4 was persistent despite subarachnoid bleeding. This is but further indication of the necessity for lumbar puncture in all neurologic conditions. On the other hand, the patient in Case 3 exhibited mild meningeal signs with an acellular spinal fluid. The spinal fluid findings in Case 5 were thought to be caused by traumatic spinal puncture and not by intracranial bleeding. It is not always possible to distinguish the bloody spinal fluid of spontaneous subarachnoid hemorrhage from that of traumatic spinal taps. However, constant red cell counts in multiple tubes, xanthochromia of the supernate and failure of the blood to coagulate are suggestive of a nontraumatic origin of the blood.

*Symptomatology:* Unusual symptomatology was manifested in all cases. In three cases, personality changes were marked. In Cases 1 and 5 acute psychotic episodes developed which were not clearly organic in appearance. In Case 4 the patient became elated and appeared unusually industrious. These cases suggest that subarachnoid hemorrhage might well be considered in patients with acute unexplained behavioral changes.

Two patients exhibited aphasia as major symptoms, although the pathogenesis appeared to differ in each case. In Case 2 the mechanism appeared to be that of the aneurysm exerting pressure as an extracerebral mass, while in Case 4 the aphasia resulted from hemorrhage into the left temporal lobe. In addition to the aphasia, the patient in Case 2 exhibited right focal seizures and left optic neuropathy, the aneurysm acting as a left subfrontal mass.

*Atypically Situated Aneurysms:* The patients in Cases 3 and 6 displayed unusual locations for the aneurysms, resulting in unusual symptoms. In Case 6 the patient had severe facial pain and unilateral ophthalmoplegia from an infraclinoid aneurysm involving the trigeminal nerve in the region of the gasserian ganglion. In Case 2 the patient exhibited bilateral symptoms which were considered to be multiple vascular episodes. However, vertebral angiography revealed an aneurysm of the posterior circulation.

Posterior circulation locations account for about one-quarter of cerebral aneurysms.[3] However, the clinical incidence is far lower. Since vertebral angiography has become more frequently employed, a much higher antemortem incidence of aneurysms in the posterior circulation has been demonstrated. In a series of sixty cases of subarachnoid hemorrhage in which no abnormality was found by bilateral carotid arteriography, Spatz and Bull[4] were able to show a vascular lesion by vertebral arteriography in 26 per cent. It is obvious that complete cerebral angiography should be performed in cases of subarachnoid hemorrhage, both for appreciation of aneurysms of unusual location and to rule out multiple aneurysms (Case 6). Multiple aneurysms were present in 27 per cent of a large series of autopsy cases.[5] Incomplete arteriography contributed to the diagnostic difficulties in Cases 1, 3 and 4.

*Dissimilar Episodes:* Two different modes of presentation separated by a significant time interval were seen in the patients in Cases 2, 4 and 6. In these cases the initial symptoms were headache (Case 4), headache and coma thought to be a "stroke" (Case 2), and internal rectus palsy thought to be related to a local eye disorder (Case 6). The intervals between initial symptoms and presentation in these cases were six weeks (Case 4), eight years (Case 2) and twenty years (Case 6).

*Diagnosis:* Each of the six patients exhibited multiple facets that detracted from the correct diagnosis of cerebral aneurysm, yet in none of the patients should this diagnosis be missed. The difficulties in attaining a correct diagnosis can only be overcome by (1) a vigilant awareness of the possibility of cerebral aneurysm in cerebral disorders, (2) a knowledge of its various modes of presentation, (3) awareness that an aneurysm is always the most likely cause of cerebral bleeding in the absence of an unequivocal explanation such as severe cranial trauma, and (4) insistence that lumbar puncture and complete angiography be performed in most cases. These points gain a particular relevance in view of recent trends to treat "vascular disease" of the brain with anticoagulants.

## Summary

Six cases of cerebral aneurysms which were diagnostic problems are presented and discussed. Bizarre symptom complexes and unusual background situations contributed to the diagnostic difficulties.

Some patients exhibited backgrounds of cardiac and vascular disease and blood coagulation defects. Two separate episodes with different symptoms were present in other cases. Unusual symptoms were dependent on unusual

size and location of the aneurysms. Acute psychotic episodes without meningeal signs were present in two patients with subarachnoid bleeding. Incomplete arteriography was another diagnostic pitfall.

The diagnosis of aneurysm should be considered prominently in all instances of subarachnoid hemorrhage and in cases suggesting a mass at the base of the brain.

## References

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# Experimental Study

# The Electrograms of the Conductive Tissue in the Normal Dog's Heart*

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It is our opinion that the electrical phenomenon of the conductive tissue of the heart has been only superficially studied, probably due to the technical difficulties that have been encountered. Coraboeuf and Weidmann[1] were the first to obtain the action potential of the Purkinje fibers in isolated preparations. We believe that Durrer and Van der Tweel[2] were the first to obtain the electrogram of the Purkinje tissue with intramural unipolar leads in the dog's heart working *in situ*. Recently, Alanís and co-workers[3] studied the electrical activity of the bundle of His using the perfused isolated heart of the dog. These authors described a diphasic potential for this structure and named it "H potential."

We have reviewed recent important work from Japan prepared by Sano,[4] Matsuda,[5,6] and co-workers. Both groups obtained similar results for the action potential of the A-V node (Tawara) although they worked independently. The following is quoted from the work of Matsuda et al.:[5]

"The characteristic features of the cellular action potential as follows were observed only in the localized area where the A-V node was known to exist. The characteristics are: (1) slow rise of depolarization; (2) definite delay of the spike from the start of depolarization amounting from 40 to 80 msec.; preceding the spike there is a slow rise simulating the synaptic potential, at times a step-like potential; (3) the overshoot is small or absent; (4) slight undershooting following the repolarization and slightly lowered resting potential."

Scher and co-workers[7] have also made studies on the action potential of the node, with a close similarity to the findings of the other investigators.

In this paper we present tracings which we believe have been obtained for the first time, corresponding to the electrical activity of the right and left branches of the bundle of His. We have also been successful in recording simultaneous activities of the different segments of the conducting tissue (node, bundle, branches and Purkinje). These experiments were performed in the dog's heart with *in situ* preparation.

## MATERIAL AND METHOD

Six dogs were used with an average weight of 11 kg. Under pentobarbital sodium anesthesia (30 mg. per kg.), the chest was opened and the heart exposed.

The electrodes consisted of tiny steel needles, about 2 inches long, completely insulated with the exception of the tip. The recording portion of the electrode was about 10 $\mu$ in diameter and about half a millimeter in length.

Bipolar leads were used placing one electrode in the segment of the conductive tissue being explored and the other at a distance of about 1 or 2 cm. The potentials were recorded with a double-beam Dumont cathode-ray oscilloscope type 322-A, previously amplified by a three-stage push-pull capacity resistance-coupled Grass pre-amplifier model P5R.

*Exploration of the Atrioventricular Node:* The tip of the needle was directed toward the posterior-inferior portion of the interatrial septum. The route followed to reach this region was through the inferior vena cava.

It is very important to locate the point of the needle precisely within the Koch's triangle limited

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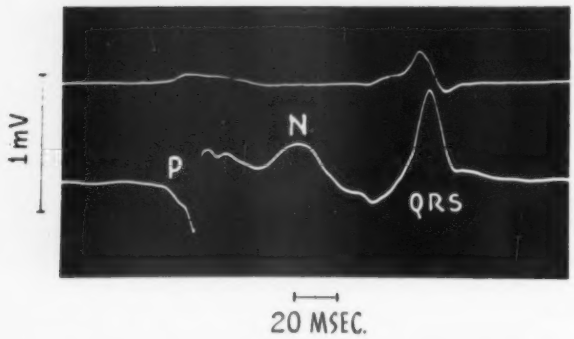


FIG. 1. Slow potential change due to the activation of the head of the A-V node (N potential) recorded with a bipolar lead. The polarity was reversed. In all figures the upper tracing corresponds to lead II.

by the following apices (structures): the fossa ovalis, the coronary orifice, and the septal and anterior cusp of the tricuspid valve. This is careful and tedious work of precision, inasmuch as no recording is obtained if the electrode is not placed exactly in the area described.

*Exploration of the Bundle of His:* In order to explore this structure it is necessary to direct the electrode toward the anterior vertex of the Koch's triangle, corresponding to the anterior and septal cusp of the tricuspid valve. No definite boundary exists between the A-V node and the bundle of His. We often think we are registering one section when actually the other is being explored.

If the exploring electrode approaches the coronary sinus (posterior vertex of the Koch's triangle) and a slow potential is recorded we can be fairly sure that we are exploring the A-V node. On the other hand, if the exploring electrode approaches the septal cusp of the tricuspid valve and a rapid electrical activity is obtained, we can then be fairly certain that it is the bundle of His we are exploring.

*Exploration of the Right Branch:* The electrode crosses the free right ventricular wall and is directed toward those regions of the septum where the right branch starts and begins to descend.

The point aimed at for the introduction of the electrode must be reached in a direct line without scratching any part of the rest of the tissue. If at the first attempt the exact point is not reached in a direct manner, the electrode must be removed and the attempt repeated. Transient right bundle branch block will not be obtained unless the electrode is introduced exactly as described. As soon as right bundle branch block appears we can rest assured that the electrode has reached its destiny in a correct manner.

*Exploration of the Left Branch:* The electrode crosses the free left ventricular wall and is directed toward those regions where the left branch starts and begins to descend. The identical precautions suggested for reaching the right branch must also be taken for reaching the left branch. We repeat, the electrode must penetrate in a direct manner and transient left bundle branch block must be obtained without scratching.

*Exploration of the Purkinje Tissue:* The electrode must be directed toward those regions where we know from anatomical studies that profusiveness exists in the Purkinje tissue, i.e., middle and lower portions of the left septal endocardium, at the apex of the heart, and at the anterior papillary muscle of the right septal surface.

The tip of the electrode must not penetrate muscle mass but must somehow hang on to the trabecular tissue.

*Proof of the Exploration of the Conductive Tissue:* This proof can be obtained by (1) looking for electrical activity in the normal P-R segment; these potential waves must be absolutely independent and distinct from the P wave and the QRS complex; (2) provoking injury with the exploring electrode; the resultant monophasic wave must be independent and distinct from the P wave and the QRS complex; it has to be located in the P-R segment; and (3) obtaining anatomical proof that the electrodes were placed in the different segments of the conductive tissue.

## RESULTS

We suggest the following terminology for the electrograms of the different portions of the specific conductive tissue:

In the A-V node: "N potential"
In the bundle of His: "H potential"*
In the right branch: "D potential"†
In the left branch: "I potential"‡
In the Purkinje arborization fibers: "A potential"§

*The Electrogram in the A-V Node (N Potential):* The activity in this structure is manifested by a slow potential change (Fig. 1), morphologically similar to the one described by Scher and co-workers.[7] The potential is negative in the head of the A-V node. In Figure 1 it is inscribed as a slow positive wave due to the

* "H" was proposed by Alanís et al.[3] for the electrogram recorded in the bundle of His.

† "D" was taken from the Spanish word "derecha" meaning "right." We thought it would not be convenient to use "R" (right in English) because it could be confused with the R wave of the clinical electrocardiogram.

‡ "I" from the Spanish word "izquierda" meaning "left."

§ "A" (from arborization) was chosen by us in preference to "P" (Purkinje) in order to eliminate confusion with the P wave of the electrocardiogram.

reversed polarity of the bipolar lead. Its duration is between 25 and 39 msec. (20 msec. according to Scher et al.). The N potential is inscribed at less than 10 msec. after the P wave in lead II when the electrode is located close to the ostium of the coronary sinus (about 3 mm.); but if the same electrode is placed at other portions of the A-V node (not in the head) the N potential is inscribed later. In Figure 2 the slow nodal potential is positive, with longer duration (around 44 msec.) and is recorded about 20 msec. after the P wave in lead II.

The slow inscription of the rising limb is characteristic of the N potential (Figs. 1 and 3). The beginning of this action potential is an upward concave curve which has been described before by Sano et al.[4] and by Matsuda and co-workers.[5]

The latter authors find great similarity between slow rise depolarization and the synaptic potential. We believe that this slow rise could be caused by the passage of the activation wave from the atrial to the nodal tissue (Fig. 3).

*The Electrogram in the Bundle of His (H Potential):* The H potential can be described as a diphasic wave similar to the one obtained by Alanís and co-workers[3] (Fig. 4). Its duration is about 20 msec. and in Figure 4 its beginning is inscribed 23 msec. after the end of the P wave in lead II.

The H potential shows a relatively rapid intrinsic deflection which can be used for the determination of the speed of the activation wave from the bundle to the right branch.

Alanís and co-workers[3] referred to the A-H subinterval measured from the beginning of the P wave to the H potential, and the H-V subinterval, measured from the H potential to the beginning of QRS. These subintervals related with lead II in Figure 4 result as follows: A-H subinterval 72 msec. and H-V subinterval 28 msec.

*The Electrogram in the Right Branch (D Potential):* The D potential is also inscribed as a diphasic wave with rapid inscription of the intrinsic deflection (Fig. 5). It appears a little after the H potential and in Figure 5 it is inscribed 26 msec. after the P wave in lead II. Its duration in the same figure is near 4 msec.; this is a more rapid phenomenon when it is compared with the one obtained in the bundle of His.

*The Electrogram in the Left Branch (I Potential):* This potential is also diphasic but not as rapid as in the right branch (Fig. 6).

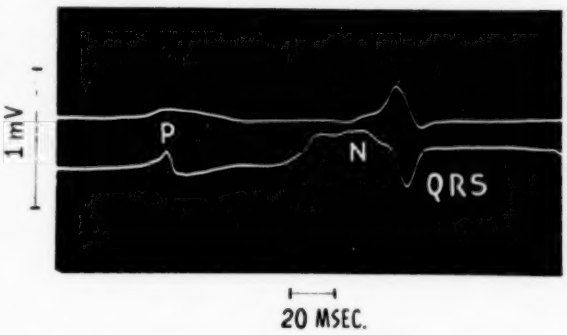


FIG. 2. Slow potential change due to the activation of the tail of the A-V node (N potential) recorded with a bipolar lead. The polarity was reversed. Note the slow inscription of the first portion of the rising limb.

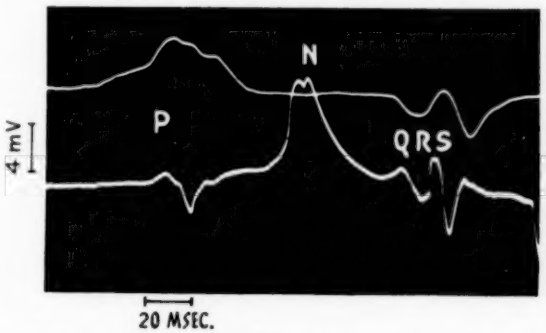


FIG. 3. Slow potential change due to the activation of the A-V node (N potential). Almost a monophasic action potential was recorded in this experiment. Note the step-like potential in the first portion of the rising limb.

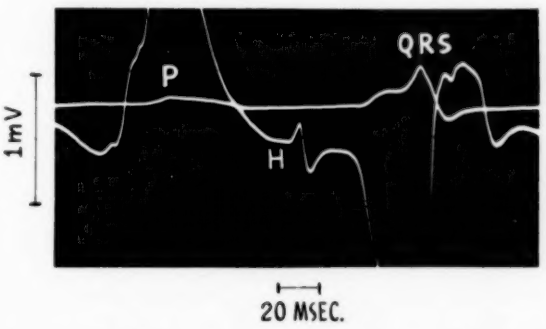


FIG. 4. Diphasic potential recorded in the bundle of His (H potential).

We found in our experiment that its inscription was simultaneous with the potential of the right branch, at 26 msec. after the end of the P wave in lead II. Its duration was 10 msec., which is smaller than that of the bundle.

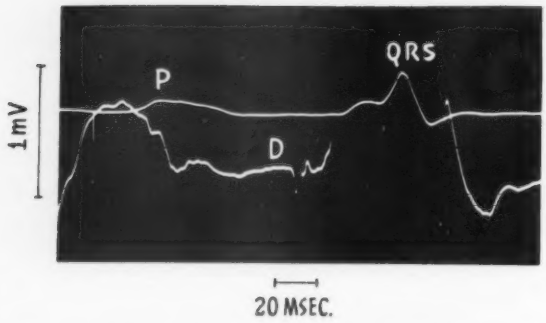


FIG. 5. Diphasic potential recorded in the right branch (D potential).

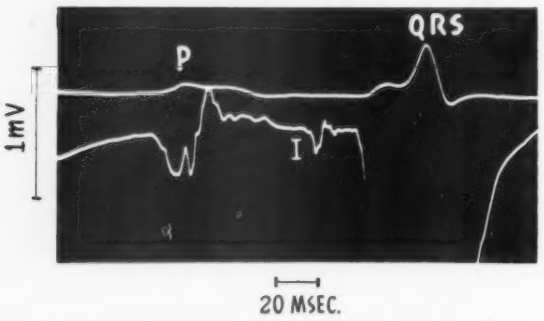


FIG. 6. Diphasic potential recorded in the left branch (I potential).

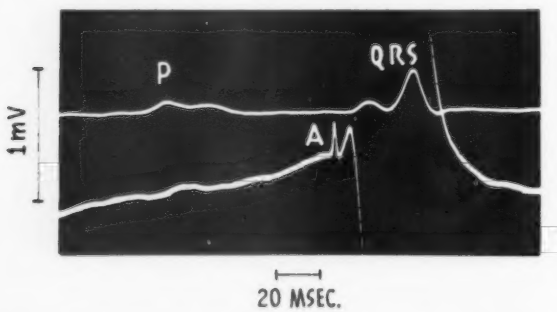


FIG. 7. Potential change recorded at the Purkinje tissue (A potential).

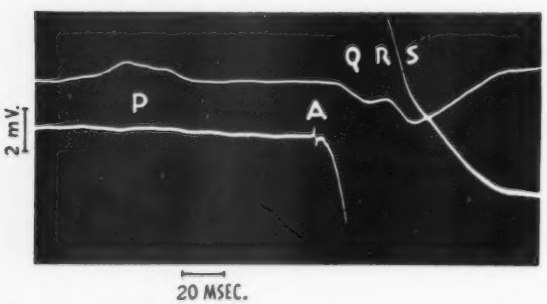


FIG. 8. Diphasic potential recorded at the Purkinje tissue (A potential).

*The Electrogram of the Purkinje Fibers (A Potential):* The potential wave that we believe is due to the Purkinje fibers* was a tiny positive deflection inscribed immediately before the QRS complex (Fig. 7). Its duration was around 3 msec. and it was recorded 40 msec. after the P wave in lead II. The time between the intrinsic deflection of the A potential and the beginning of the QRS complex in lead II was close to 7 msec. and that time would be shorter if we use the beginning of QRS in the direct lead for this calculation.

Our tracings are similar to those published by Durrer.[2] They differ only in the morphology for the A potential which is diphasic in Durrer's paper. This difference in morphology could be explained by the presence of a slight injury produced by the exploring electrode in our experiment, which could have also been the cause for the disappearance of the negative deflection in our tracing. In other more recent experiments our tracings are identical to those published by Durrer (Fig. 8).

*The Speed of Conduction between the Bundle of His and the Right Branch:* The exploring electrode located in the bundle of His was separated by 15 mm. from the one in the right bundle. Both tracings were obtained simultaneously (Fig. 9) and the speed of conduction calculated by using the intrinsic deflection of both tracings was 2,656 mm. per sec. We had expected these high figures from this type of tissue. Other speeds calculated for the same type of tissues are 4,400 and 3,827 mm. per sec.

*Speed of Conduction between the Left Bundle and*

* Unpublished data.

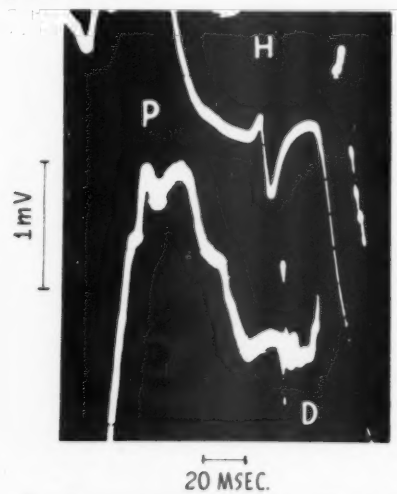


FIG. 9. Simultaneous recording of the H potential and D potential.

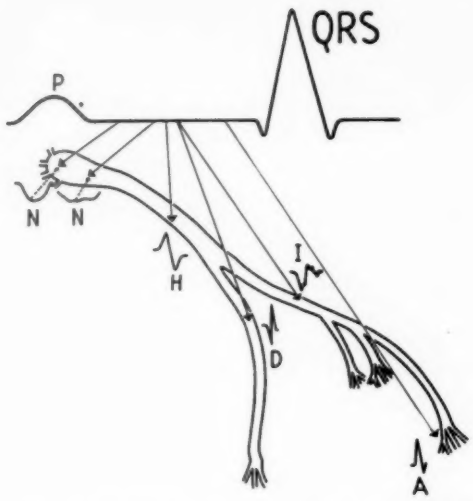


FIG. 10. Relationship of the different potentials recorded in the specific tissue to lead II.

*the Purkinje's Fibers:* The two corresponding electrodes were separated 29.5 mm. and the speed calculated was 2,107 mm. per sec., a figure similar to the one between the bundle of His and the right branch.

*Simultaneous Activation of Both Branches:* The right and the left branches were activated simultaneously 26 msec. after the P wave in lead II. This brings up the question as to why the left septal surface is activated before the right.

*Relationship of the Potentials Recorded in the Specific Tissue to Lead II:* Figure 10 shows the potential recorded at several sites in the specific tissues. The one obtained in the head of the A-V node (N wave in Fig. 10) is inscribed a little after the P wave and precedes by 11 msec. the one obtained in the tail of the A-V node (N wave in Fig. 10). The H potential is inscribed in the middle of the P-R segment and this potential precedes by 3 msec. the inscription of the D and I waves. Almost at the end of the P-R segment we recognize the electrical activity of the Purkinje tissue (A potential) 7 msec. before the beginning of QRS in lead II.

## COMMENTS

The recording of the electrical activity of the conductive tissue opens wide fields of investigation. The study of different arrhythmias, such as auricular and ventricular premature beats and the so-called nodal rhythms, and the mechanism of bundle branch block, A-V block and interference dissociation, would not be complete until we learn more about the role of the different structures of the specific tissues in all these alterations. Moreover, the action of different drugs such as digitalis, adrenalin and quinidine will be more precisely studied.

In the near future we may be able to answer the following questions: At what level does the digitalis action determine A-V block? Is it within the node? Is it at the point of passage of the stimulus from the auricular tissue to the node?

In relation to the sequence of the activation process of the heart many other questions can also be answered. Is there a latency period between the activation of the Purkinje fibers and the depolarization of the muscle fibers close by? Can one stimulus ascending by a branch descend by the other? In cases of bundle branch block at what level does the activation wave reach the branch of the blocked side?

These are questions that concern us as electrocardiologists and are presented as points of orientation for future research.

## SUMMARY

Simultaneous recording of electrograms of the A-V node, bundle of His, right and left branches and the Purkinje tissue was successfully achieved and is herein presented. The speed of the activation wave in some segments of this specific tissue is calculated. A few considerations for future research are also made.

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# Reports on Therapy

## Further Observations on Flumethiazide

### A New Oral Diuretic Agent*

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IN A PREVIOUS paper, flumethiazide† was reported to be an effective diuretic agent as determined by weight response in ambulatory patients with cardiac disease.[1] Comparative potency and dose range studies were also reported. Preliminary observations indicated that the agent has a marked diuretic and natruretic effect and a slight effect on potassium excretion. Because of these observations, we have undertaken the following study of the effect of this drug on renal hemodynamics and on electrolyte excretion in acute and chronic experiments.

#### MATERIALS AND METHODS

*Observations on Renal Hemodynamics:* The acute diuretic response to flumethiazide was observed in patients with cardiac disease selected from the wards of the Hahnemann Hospital. Those with impaired renal function due to primary renal disease were excluded. The patients were stabilized on a standard daily diet containing 2,500 calories and an intake of 2,000 to 3,000 cc. of fluid for several days. The salt intake was constant for each patient but varied from patient to patient. Diuretics were not given during the control period. The patients were weighed after overnight fasting prior to the experiment. Urine volume, sodium and potassium excretion rates, glomerular filtration rate, renal plasma flow, and plasma concentrations of sodium, potassium and creatinine were then determined using urine collection periods of twenty minutes each. Glomerular filtration rate and renal plasma flow were estimated by the inulin and para-aminohippuric acid clearance technics as described by Roe[2] and by Smith et al.,[3] respectively. Sodium and potassium concentrations were determined by use of the Beckman flame photometer (direct reading).

After the control studies were completed, 800 mg. of flumethiazide were given orally to seven patients. Half hourly or hourly urine collections were made for four to seven hours. Urine volume, renal hemodynamics and electrolyte excretion rates were determined as during the control periods. One patient (Case 7) included in this group received also 2,000 mg. of flumethiazide orally one week after the aforementioned studies. Another patient (Case 8) received a trial dose of 1,000 mg. given intravenously over a period of twenty minutes. The drug was dissolved in 5 per cent glucose in water for this purpose. Hematocrits and blood pressures were measured during each collection period.

*Observations on Electrolyte Excretion During Six Days of Drug Administration:* The chronic diuretic effect of flumethiazide was observed in hospitalized patients kept on a 2,500 calorie diet and an intake of approximately 3,000 cc. of fluids daily. Here again the salt intake was constant for each patient but varied from patient to patient. Sodium, potassium and creatinine excretion rates were determined. Creatinine determinations were made to insure that accurate twenty-four-hour collections of urine had been obtained before and after drug administration. Usually four to five days were allowed for stabilization of the electrolyte excretion. Five patients received 800 mg. of flumethiazide twice daily, five patients received 1,000 mg. twice daily and another six patients were given 1,000 mg. daily for six days. These patients were suffering from compensated arteriosclerotic heart disease. No gross renal functional derangement was present in any patient as confirmed by laboratory tests. One patient not included in these series, who had advanced chronic glomerulonephritis, was given the drug but failed to show any diuretic response.

* From the Department of Medicine, Hahnemann Medical College and Hospital, Philadelphia, Pennsylvania.
† 6-Trifluoromethyl-7-sulfamyl-1,2,4-benzothiadiazide-1,1-dioxide. Supplied as Ademol® by E. R. Squibb & Sons, New Brunswick, New Jersey.

TABLE I

Renal Hemodynamic Response to Flumethiazide

| Case No., Age (yr.) and Sex | Mean Blood Pressure (mm. Hg) | | | | | | | Glomerular Filtration Rate (cc./min.) | | | | | | | Renal Blood Flow (cc./min.) | | | | | | | Hematocrit | | | | | | | Weight (kg.) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | C | $D_1$ | $D_2$ | $D_3$ | $D_4$ | $D_5$ | $D_6$ | C | $D_1$ | $D_2$ | $D_3$ | $D_4$ | $D_5$ | $D_6$ | C | $D_1$ | $D_2$ | $D_3$ | $D_4$ | $D_5$ | $D_6$ | C | $D_1$ | $D_2$ | $D_3$ | $D_4$ | $D_5$ | $D_6$ | |
| *800 mg. of Flumethiazide Orally* | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 1, 73, F. | 150 | 125 | 136 | 136 | 140 | .. | .. | 87 | 90 | 82 | 91 | 89 | .. | .. | 810 | 1091 | 840 | 860 | 800 | .. | .. | 47 | 46 | 46 | 46 | 47 | .. | .. | 63 |
| 2, 45, F. | 93 | 94 | 93 | 86 | 80 | 90 | 91 | 76 | 68 | 73 | 92 | 70 | 61 | 76 | 553 | 509 | 596 | 563 | 533 | 564 | 594 | 36 | 35 | 35 | 34 | 36 | 36 | 36 | 70 |
| 3, 40, F. | 95 | 91 | 95 | 89 | 94 | 98 | .. | 48 | 48 | 57 | 58 | 65 | 48 | 53 | 543 | 416 | 479 | 484 | 525 | 507 | .. | 42 | 39 | 38 | 39 | 38 | 39 | .. | 50 |
| 4, 42, F. | 116 | 146 | 148 | 147 | 130 | 136 | .. | 56 | 55 | 56 | 65 | 65 | 50 | .. | 713 | 688 | 627 | 680 | 713 | 714 | .. | 48 | 50 | 52 | 53 | 57 | 52 | .. | 90 |
| 5, 42, F. | 83 | 86 | 92 | 93 | 91 | 90 | .. | 88 | 83 | 85 | 86 | 84 | 89 | .. | 652 | 696 | 672 | 605 | 683 | 658 | .. | 33 | 33 | 33 | 34 | 33 | 34 | .. | 54 |
| 6, 44, F. | 90 | 89 | 90 | 86 | 97 | 92 | .. | 56 | 62 | 59 | 60 | 55 | 61 | .. | 450 | .. | 424 | 456 | 462 | 436 | .. | 32 | 32 | 32 | 31 | 30 | 30 | .. | 56 |
| 7, 37, F. | 87 | 88 | 89 | 89 | 85 | 84 | 83 | 71 | 76 | 73 | 71 | 67 | 79 | 85 | 558 | 474 | 432 | 450 | 460 | 580 | 625 | 41 | 41 | 40 | 40 | 41 | 41 | 42 | 59 |
| Average... | 102 | 103 | 106 | 104 | 102 | 98 | .. | 69 | 69 | 69 | 75 | 69 | 65 | .. | 610 | 645 | 581 | 585 | 596 | 576 | .. | 40 | 39 | 39 | 39 | 40 | 39 | 39 | .. |
| *2,000 mg. of Flumethiazide Orally* | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 7, 37, F. | 84 | 79 | 78 | 84 | 90 | 91 | 90 | 73 | 71 | 76 | 75 | 67 | 68 | 64 | 638 | 610 | 595 | 632 | 616 | 640 | 640 | 41 | 41 | 39 | 39 | 38 | 39 | 39 | 59 |
| *1,000 mg. of Flumethiazide Intravenously** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 8, 53, F. | 89 | 86 | 88 | † | .. | .. | .. | 78 | 62 | 66 | † | .. | .. | .. | 541 | 533 | 485 | .. | .. | .. | .. | 41 | 38 | 39 | .. | .. | .. | .. | 65 |

C = Control observations: average of three twenty-minute periods. $D_1$–$D_6$ = Observations one to six hours after drug administration (one-hour periods).

* Injected in twenty minutes in 5 per cent dextrose in water.

† Discontinued due to technical difficulty.

## Results

*Observations on Renal Hemodynamics:* The results of the study are tabulated in Tables I and II. Following the oral administration of 800 mg. of flumethiazide to seven patients, the excretion rate of sodium showed a slight increase after one hour which was not statistically significant. After two hours there was a marked natruresis which persisted in excess of six hours. This natruresis was statistically significant with a probability value ($p$ value) of less than 0.02 at two hours, less than 0.01 at three hours, less than 0.02 at four hours and less than 0.01 at five hours. Thus the effect of the drug was manifested within one to two hours after administration, and even five hours after administration there was no indication of a reduction in response. Unfortunately, it was not advisable from the standpoint of patient comfort to continue the experiment further.

There was a pronounced increase in urine volume which paralleled the natruretic response (Table II). Even as early as one hour after drug administration, there was a significant increase in urine volume ($p < 0.01$). The increase over control level became progressively larger throughout the five-hour period after drug administration. Potassium excretion did not appear to be affected appreciably.

There was no evidence of any consistent pattern with respect to renal hemodynamics (Table I). These included glomerular filtration rate, renal plasma flow, mean blood pressure and hematocrit. Plasma sodium and potassium levels were not altered.

In one patient (Case 7) 800 and 2,000 mg. of flumethiazide were given on two different occasions. There was no significant effect on the renal hemodynamics, mean blood pressure, and plasma sodium and potassium levels. It is noteworthy that while the double dose induced elevated natruresis, there was no marked difference in the potassium excretion patterns. In both instances the potassium excretion remained quite close to the pretreatment levels. After 800 mg. of flumethiazide the urine sodium excretion rose to a level more than twice as high as the control level, and approximately the same was true for the urine volume. After 2,000 mg. of flumethiazide the urine volume increased threefold and the sodium excretion increased fourfold, but the control excretion rate of sodium was only 49 mEq./min. as compared to 170 mEq./min. during the control period for the 800 mg. dose of flumethiazide.

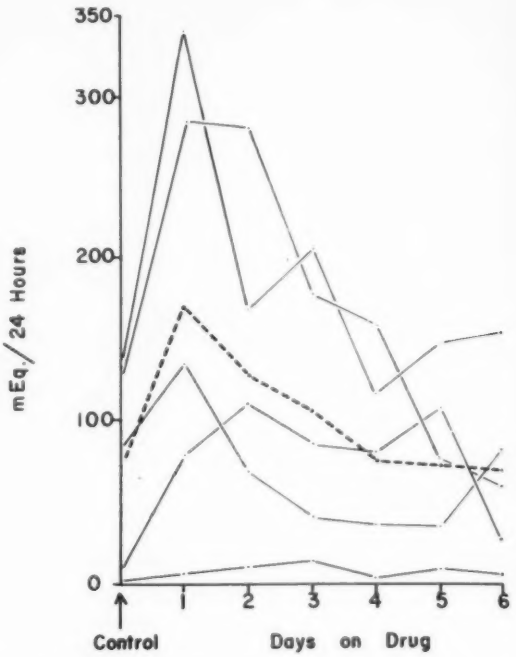


Fig. 1. Effect on daily sodium excretion of 800 mg. of flumethiazide given twice a day for six days is shown in five patients. There is a significant increase in sodium excretion during the first two days. The control values were again reached after four to six days. This is probably the result of relative sodium depletion and reaching the "dry weight." Solid lines indicate individual patients; dotted line indicates mean value.

*Observations on Electrolyte Excretion During Continuous Daily Administration of Flumethiazide:* The results of the chronic studies in hospitalized patients kept on a standard fluid and salt intake are shown in Figure 1 and Table III. There was a prompt natruretic response to flumethiazide during the first day and a peak was reached usually during the first two days. After four to five days the sodium excretion fell to control levels. Water diuresis paralleled the sodium excretion in these patients. Although these observations were not made under rigid metabolic control, the results indicate that the patients failed to continue their natruresis after several days during which time a significant response was observed. However, the patients were maintained at the "dry weight" following this phase of the drug effect.

## Comments

Flumethiazide is a new member of the sulfamyl benzothiazide group of diuretics. It appears from our experiments that the glomerular filtration rate and renal plasma flow are

## TABLE II

### Effect of Flumethiazide on Water and Electrolyte Excretion

| Case No. | Urine Volume (cc./min.) | | | | | | | Sodium Excretion (μEq./min.) | | | | | | | Potassium Excretion (μEq./min.) | | | | | | | Plasma Sodium (mEq./L.) | | | | | | | Plasma Potassium (mEq./L.) | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | C | $D_1$ | $D_2$ | $D_3$ | $D_4$ | $D_5$ | $D_6$ | C | $D_1$ | $D_2$ | $D_3$ | $D_4$ | $D_5$ | $D_6$ | C | $D_1$ | $D_2$ | $D_3$ | $D_4$ | $D_5$ | $D_6$ | C | $D_1$ | $D_2$ | $D_3$ | $D_4$ | $D_5$ | $D_6$ | C | $D_1$ | $D_2$ | $D_3$ | $D_4$ | $D_5$ | $D_6$ |
| *800 mg. of Flumethiazide Orally* | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 1 | 1.0 | 1.9 | 1.2 | 1.2 | 0.9 | .. | .. | 14 | 19 | 53 | 70 | 63 | .. | .. | 74 | 106 | 114 | 112 | 103 | .. | .. | 154 | 154 | 154 | 155 | 154 | .. | .. | 2.4 | 3.2 | 3.4 | 3.3 | 3.0 | .. | .. |
| 2 | 1.0 | 2.3 | 2.2 | 2.6 | 4.1 | 4.4 | 3.2 | 294 | 513 | 454 | 487 | 672 | 550 | 825 | 116 | 76 | 77 | 119 | 75 | 88 | 75 | 146 | 148 | 148 | 147 | 149 | 150 | 149 | 3.4 | 4.5 | 4.6 | .. | 4.5 | 5.2 | 4.4 |
| 3 | 1.1 | 1.3 | 1.5 | 1.8 | 1.8 | 1.6 | .. | 162 | 141 | 138 | 141 | 139 | 137 | .. | 57 | 34 | 38 | 34 | 32 | 30 | .. | 139 | 141 | 138 | 141 | 139 | 137 | .. | 3.9 | 4.1 | 3.8 | 4.1 | 3.9 | 4.0 | .. |
| 4 | 1.6 | 1.7 | 2.0 | 2.0 | 2.0 | 2.0 | .. | 145 | 219 | 467 | 460 | 435 | 438 | .. | 43 | 63 | 84 | 100 | 106 | 75 | .. | 149 | 146 | 146 | 144 | 147 | 144 | .. | 4.6 | 4.8 | 4.6 | 4.5 | 4.5 | 4.4 | .. |
| 5 | 1.0 | 1.0 | 2.1 | 2.1 | 1.9 | 3.8 | .. | 138 | 161 | 407 | 470 | 473 | 491 | .. | 64 | 85 | 95 | 52 | 33 | 31 | .. | 140 | 141 | 137 | 134 | 135 | 138 | .. | 4.1 | 4.0 | 3.9 | 3.7 | 3.6 | 3.6 | .. |
| 6 | 0.4 | 0.7 | 1.5 | 1.8 | 2.1 | 1.9 | .. | 90 | 76 | 144 | 367 | 408 | 415 | 466 | 13 | 17 | 27 | 28 | 31 | 31 | .. | 142 | 139 | 137 | 134 | 135 | 137 | .. | 3.3 | 3.2 | 3.1 | 3.1 | 3.1 | 3.7 | .. |
| 7 | 1.1 | 1.2 | 2.2 | 2.5 | 2.2 | 2.0 | 1.8 | 170 | 270 | 384 | 390 | 380 | 403 | 386 | 46 | 36 | 42 | 37 | 30 | 25 | 26 | 147 | 147 | 148 | 149 | 146 | 147 | 147 | 4.5 | 4.2 | 4.8 | 5.2 | 4.3 | 4.4 | 4.3 |
| Average | 1.0 | 1.4 | 1.8 | 2.0 | 2.1 | 2.6 | .. | 145 | 200 | 292 | 341 | 367 | 406 | .. | 59 | 60 | 68 | 69 | 59 | 47 | .. | 145 | 145 | 144 | 143 | 143 | 142 | .. | 3.7 | 4.0 | 4.0 | 4.0 | 3.9 | 4.3 | .. |
| P. value < | .. | 0.01 | 0.01 | 0.01 | 0.05 | 0.05 | .. | .. | N.S. | 0.02 | 0.01 | 0.02 | 0.01 | .. | .. | N.S. | N.S. | N.S. | N.S. | N.S. | .. | .. | N.S. | N.S. | N.S. | N.S. | N.S. | .. | .. | N.S. | N.S. | N.S. | N.S. | N.S. | .. |
| *2,000 mg. of Flumethiazide Orally* | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 7 | 0.6 | 1.2 | 1.8 | 1.6 | 1.5 | 1.5 | 1.5 | 49 | 84 | 168 | 185 | 218 | 243 | 234 | 63 | 67 | 77 | 75 | 66 | 50 | 43 | 145 | 145 | 145 | 145 | 146 | 147 | 148 | 3.3 | 3.4 | 3.2 | 3.2 | 3.2 | 3.2 | 3.5 |
| *1,000 mg. of Flumethiazide Intravenously** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 8 | 0.8 | 4.0 | 3.7 | † | .. | .. | .. | 50 | 270 | 283 | .. | .. | .. | .. | 19 | 46 | 48 | .. | .. | .. | .. | 145 | 144 | 144 | .. | .. | .. | .. | 3.8 | 3.4 | 3.6 | .. | .. | .. | .. |

C = Control observations: average of three twenty-minute periods. $D_1$–$D_6$ = Observations one to six hours after drug administration (one-hour periods). N.S. = Not significant.

* Injected in twenty minutes in 5 per cent dextrose in water.

† Discontinued due to technical difficulty.

TABLE III

Effect of 1,000 Mg. of Flumethiazide Given Daily* and Twice Daily for Six Consecutive Days on Twenty-four-Hour Sodium and Potassium Excretion Rates

| Case No. | Drug Administration | Sodium Excretion (mEq./24 hr.) | | | | | | | Potassium Excretion (mEq./24 hr.) | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Days Receiving Drug | | | | | | | Days Receiving Drug | | | | | | |
| | | C | 1 | 2 | 3 | 4 | 5 | 6 | C | 1 | 2 | 3 | 4 | 5 | 6 |
| 1 | Daily | 55 | 111 | 165 | 82 | 104 | 59 | 32 | 40 | 38 | 59 | 61 | 68 | 68 | 53 |
| | Twice daily | 17 | 79 | 110 | 85 | 80 | 109 | 28 | 23 | 22 | 53 | 40 | 44 | 50 | 38 |
| 2 | Daily | 8 | 48 | 26 | 34 | 41 | 9 | 13 | 27 | 27 | 26 | 28 | 26 | 20 | 25 |
| | Twice daily | 134 | 339 | 167 | 207 | 114 | 147 | 157 | 78 | 97 | 91 | 107 | 108 | 115 | 85 |
| 3 | Daily | 37 | 85 | 88 | 63 | 141 | 104 | 52 | 49 | 42 | 55 | 41 | 53 | 56 | 43 |
| | Twice daily | 127 | 286 | 280 | 176 | 155 | 182 | 160 | 52 | 66 | 67 | 59 | 77 | 85 | 77 |
| 4† | Daily | 127 | 437 | 265 | 117 | .. | .. | .. | 55 | 86 | 71 | 83 | .. | .. | .. |
| | Twice daily | 43 | 136 | 68 | 40 | 38 | 37 | 83 | 40 | 75 | 73 | 64 | 64 | 61 | 92 |
| 5 | Daily | 84 | 171 | 138 | 89 | 120 | 78 | 73 | 39 | 33 | 50 | 47 | 35 | 42 | 38 |
| | Twice daily | 3 | 8 | 10 | 16 | 4 | 11 | 8 | 6 | 8 | 11 | 12 | 13 | 18 | 10 |
| 6† | Daily | 55 | 99 | 97 | 91 | .. | .. | .. | 32 | 38 | 31 | 34 | .. | .. | .. |
| | Mean: | | | | | | | | | | | | | | |
| | Daily | 46 | 104 | 104 | 67 | 102 | 62 | 42 | 39 | 35 | 48 | 44 | 46 | 46 | 40 |
| | Twice daily | 64 | 170 | 127 | 105 | 78 | 97 | 87 | 40 | 54 | 59 | 56 | 61 | 66 | 60 |

C = Control observation: average of four twenty-four-hour collection periods. Days = Days receiving drug (twenty-four-hour urine collection periods).

* Patients also received 2.0 gm. of potassium chloride orally daily.

† Not included in the mean.

not altered even in doses larger than the therapeutically effective dose of the drug. This suggests that the diuretic effect is exerted through the tubules, by inhibiting sodium and water reabsorption. Direct hypotensive effect was not noted by a single dose of flumethiazide when given either orally or intravenously. These observations parallel the properties of chlorothiazide. Plasma electrolyte levels were not appreciably altered by single or repeated doses. This was also evident during prolonged use of the drug in ambulatory patients on normal diets. The insignificant potassium loss observed is a welcome phenomenon following administration of this compound. Administration of potassium was not necessary in our patients.

Side effects were reported previously.[1] No unpleasant effects were noted in the present group of patients when the single dose did not exceed 1,000 mg. Nausea and gastric discomfort were noted after giving a single dose of 2,000 mg. to two elderly patients. This was eliminated promptly by reducing the dose to 1,000 mg. given twice a day. The lack of sustained sodium excretion after prolonged administration of the drug would suggest that relative sodium depletion had occurred. The prompt diuretic effect noted after the agent was given intravenously and its lack of toxicity suggest the possible use of this drug in conditions in which prompt diuresis is life-saving.

The therapeutic efficiency and the minimal kaliuretic effect makes this drug a valuable addition to the armamentarium for the management of edematous patients.

## Summary

1. Flumethiazide (Ademol) is an orally effective saluretic agent of the sulfamyl benzothiazide group of chemical compounds.

2. The main effect of flumethiazide is on sodium, chloride and water excretion. Significant effects on potassium excretion were not observed.

3. Renal hemodynamics did not seem to be altered when doses not exceeding 2,000 mg. were given.

4. The maximum effect of continuous daily administration is reached within the first two

days, and this is followed by gradual return of natruresis to the control level within four to six days.

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# Long Term Anticoagulant Therapy

## A Six-Year Study of an Indandione Derivative*

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DURING the past few years the use of anticoagulants in certain vascular diseases has become widespread. Today, the practice of medicine demands that all physicians, particularly internists, be familiar with their use. Many clinical studies[1–9] on the value of anticoagulants have established their usefulness for treatment of specific diseases. Most patients with thrombophlebitis and myocardial infarction receive anticoagulant therapy during the acute phase of the disease, especially when hospitalized. As a rule, however, administration of the anticoagulant is discontinued when the episode subsides or when the patient is discharged from the hospital, even though the disease process has not completely abated. It seemed to us that it would be better for the patient if administration of the anticoagulant were continued for a longer period, that is, until the disease process had more completely healed. In addition, the prolonged use of anticoagulants for prophylactic purposes warrants consideration.

When this study was begun in February 1952, the available information indicated that some anticoagulants would cause a wide fluctuation in the prothrombin time and would require too frequent checking of it to warrant their use over a long period in ambulatory patients. We believed that if anticoagulant therapy was to be used in ambulatory patients, the drug selected should be one that did not produce wide fluctuation in the prothrombin time and, therefore, would be relatively safe. The work of Jacques,[10] Blaustein[4] and others suggested that phenindione might be suitable but we believed further study of the compound was necessary before we could advocate its use in long term anticoagulant therapy.

### MATERIALS AND METHODS

At the beginning of our study (February 1952) phenindione was used only in hospitalized patients, usually those with some form of peripheral vascular disease or myocardial infarction, and daily prothrombin time determinations were made. Later, administration of the drug was continued in some patients who had been discharged from the hospital, and the prothrombin time was checked two or three times each week until we were convinced that wide variations in the prothrombin time did not occur with its use—other factors being equal. In hospitalized patients, in whom the prothrombin time was determined frequently, large doses, 300 to 400 mg. the first day and 200 to 300 mg. the second, were given to obtain quick results. The dosage schedule varied, and the maintainance dose was determined for each individual, but the average maintenance dose necessary to maintain the prothrombin at a good therapeutic level (two to two and one half times the control) was from 50 to 100 mg. daily. In patients with acute episodes of thrombophlebitis, myocardial infarction and other thromboembolic disorders, the prothrombin time was maintained at two to two and one-half times the control. When these patients recovered from the acute phase and were discharged or became ambulatory, in most instances the prothrombin time was kept at only one and one-half to one and three-quarters times the control.

In ambulatory or clinic patients, when anticoagulant therapy was indicated and the maintenance dose had not previously been determined, 20 mg. twice daily was given. The prothrombin time was checked weekly, and the dose was then adjusted until the desired therapeutic level was attained. After this the prothrombin time was determined every one to three weeks as indicated. The total daily dose was divided into two or three doses. The

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This study was supported by a grant-in-aid by Walker Laboratories. The preparation used was Hedulin,® a brand of phenindione (also known as phenylindandione or 2-phenyl-1,3-indandione).

TABLE I

Anticoagulant Therapy in Control Patient (Man, Aged Forty-Six) with Rheumatoid Arthritis

| Date | Prothrombin Time (sec.) | | Daily Dose of Phenindione (mg.) |
|---|---|---|---|
| | Control | Patient | |
| 1/21/55 | 12 | 13 | 60 |
| 1/26 | 15 | 21 | 60 |
| 2/9 | 13.5 | 20.5 | 60 |
| 2/16 | 12 | 21.5 | 60 |
| 2/23 | 13.5 | 19 | 60 |
| 3/2 | 13.5 | 19 | 60 |
| 3/9 | 14 | 19.5 | 60 |
| 3/23 | 12.5 | 19 | 60 |

anticoagulant was not given if there was a history of duodenal ulcer or of ulcerative colitis.

Simplastin®* and protrol* were used in the prothrombin time determinations and were very satisfactory.

## Toxicity

In a six-year study on over 300 patients there were only two instances of significant bleeding. One followed the extraction of a tooth in an ambulatory patient who had the extraction without our knowledge. In the second case, hematuria occurred in a patient who unintentionally increased the dose from 60 to 150 mg. of phenindione daily. With the use of vitamin $K_1$ and the omission of the anticoagulant, macroscopic bleeding subsided within thirty hours and microscopic bleeding within sixty hours. There was one instance of mild bleeding from hemorrhoids. This patient gave a history of previous bleeding from the same source but stated that the bleeding in this attack was greater than in the previous one. One patient with congestive heart failure and an anginal syndrome following myocardial infarction exhibited a mild hemoptysis following a severe attack of coughing. There were no instances of intolerance to the drug and no other side reactions were noted.

## Results

Therapeutic effects were obtained within eighteen to twenty-four hours. The prothrombin time usually returned to normal forty to sixty hours after the medication was omitted. The average maintenance dose varied in different patients but for the great majority it was between 50 and 100 mg. daily. A few patients required a maintenance dose above 100 mg. Some, however, maintained a normal prothrombin time even though they received 100 mg. daily, while 40 to 60 mg. in others maintained the prothrombin time two to two and one-half times the control. However, once the dose for each was determined, there was little fluctuation in the prothrombin time or the dosage necessary to maintain this at the desired level. Representative protocols of patients receiving phenindione are presented in Figures 1 and 2 and Tables I to VIII. Space does not permit the listing of all prothrombin times taken on these patients; however, the widest variations are included in those listed.

Figure 1 shows the record of a patient maintained

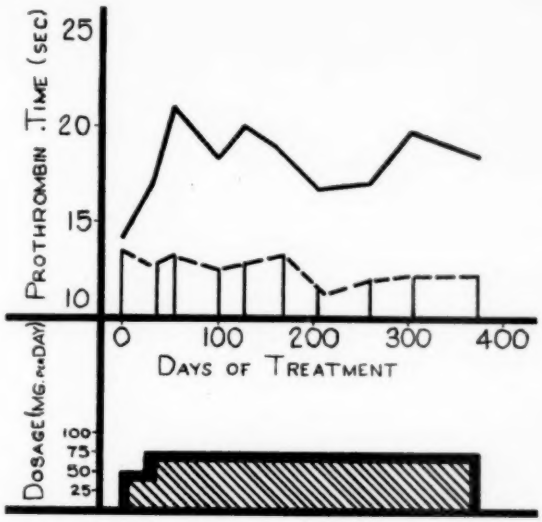


FIG. 1. Results of long term anticoagulant therapy with phenindione from December 1953 to January 1955 in a fifty-four year old patient with myocardial infarction. On a daily dose of 75 mg. the widest variation in prothrombin time was from 16.8 to 21 seconds. Solid line represents patient. Dotted line represents control subject.

TABLE II

Anticoagulant Therapy in Control Patient (Man, Aged Fifty-Nine) with Rheumatoid Arthritis

| Date | Prothrombin Time (sec.) | | Daily Dose of Phenindione (mg.) |
|---|---|---|---|
| | Control | Patient | |
| 1/4/54 | 13.2 | 13.5 | 75 |
| 1/15 | 12.8 | 20.2 | 75 |
| 1/22 | 12.8 | 24.0 | 75 |
| 1/29 | 13.3 | 21.3 | 75 |
| 2/5 | 12.7 | 20.8 | 75 |
| 2/11 | 13.2 | 20.6 | 75 |
| 2/18 | 12.2 | 16.7 | 75 |
| 3/5 | 13.8 | 17.7 | 75 |
| 3/12 | 13.5 | 19.1 | 75 |
| 3/19 | 12.5 | 19 | 75 |

* Simplastin and protrol were furnished by Warner-Chilcott Laboratories, Inc., Morris Plains, New Jersey.

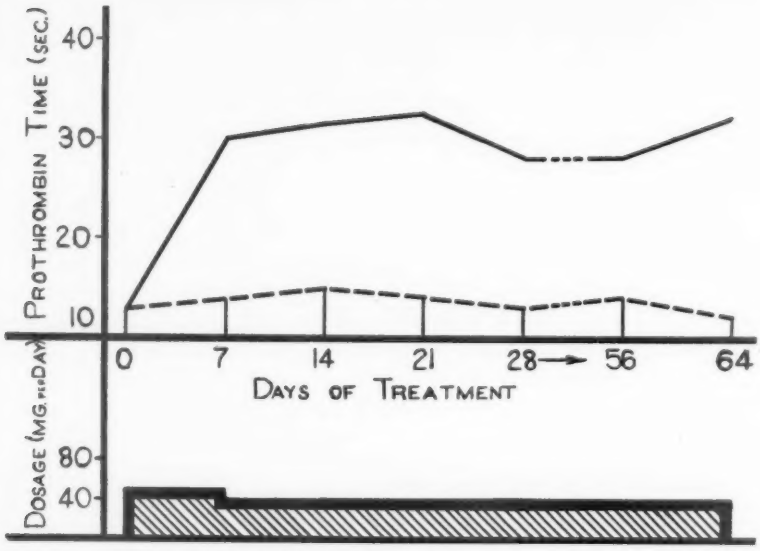


FIG. 2. Results of phenindione therapy for sixty-four days in a sixty-five year old patient with myocardial infarction. Uniform prothrombin times (two and one-half times control) were maintained with divided doses totaling 40 mg. daily. Solid line represents patient. Dotted line represents control subject.

on phenindione for over one year after being discharged from the hospital following myocardial infarction. We did not try to maintain the prothrombin at what is usually considered the therapeutic level. Figure 2 shows the record of a patient with myocardial infarction whose prothrombin time was maintained at two to two and one-half times the control during his hospital stay and five weeks thereafter. These two patients demonstrate the uniformity of action of phenindione and the lack of fluctuation in the prothrombin time whether maintained at low or therapeutic levels.

Tables I and II are the protocols of two control subjects with rheumatoid arthritis but no thromboembolic phenomena. The prothrombin time was purposely maintained at only one and one-half times the control. It remained relatively constant with no wide fluctuations and on relatively small doses, 60 and 75 mg. daily. Table III shows the results in a patient whose prothrombin time was maintained at one and one-half times normal for more than one year on 75 mg. daily. There were no wide fluctuations but a reasonably constant prothrombin time during the entire period. These three tables demonstrate that once the maintenance dose is determined, there is little variation in the prothrombin time. This factor makes it a relatively safe drug in long-continued anticoagulant therapy of ambulatory patients.

Table IV shows the results in a patient with thrombophlebitis who received a fairly large dose of phenindione (120 mg. daily from May 14, 1955 to January 29, 1956), yet at no time was the prothrombin time twice the control. It remained constant, however, varying only from 16.0 to 21.4 seconds in this period. It is also interesting to note that 50 mg. daily in the beginning increased the prothrombin time to 20.1 seconds, whereas 120 mg. daily increased it only to a high of 21.4 on July 9, 1955, about two months later; with the same dose about five months later, the prothrombin time was 19.5 seconds. When the dose was reduced to 75 mg. daily, the prothrombin time was reduced from 19.5 to 18.3 seconds.

Table V shows the results in a patient with myo-

TABLE III

Long Term Anticoagulant Therapy in Control Patient (Woman, Aged Thirty-Five) with Rheumatoid Arthritis

| Date | Prothrombin Time (sec.) | | Daily dose of Phenindione (mg.) |
|---|---|---|---|
| | Control | Patient | |
| 12/11/55 | 12.8 | 13.5 | 50 |
| 12/18 | 15.5 | 23.2 | 50 |
| 1/15/56 | 12.8 | 17.2 | 75 |
| 1/29 | 13.3 | 18.3 | 75 |
| 2/11 | 13.2 | 21.0 | 75 |
| 3/26 | 12.4 | 18.4 | 75 |
| 4/23 | 12.6 | 20.0 | 75 |
| 6/4 | 13.2 | 19.2 | 75 |
| 7/15 | 11.4 | 16.8 | 75 |
| 9/9 | 12.0 | 17.2 | 75 |
| 10/22 | 12.3 | 19.9 | 75 |
| 1/28/57 | 14.1 | 18.6 | 75 |

TABLE IV

Long Term Anticoagulant Therapy in Thirty-Three Year Old Man with Thrombophlebitis

| Date | Prothrombin Time (sec.) | | Daily Dose of Phenindione (mg.) |
|---|---|---|---|
| | Control | Patient | |
| 12/11/54 | 16.8 | 17.0 | 50 |
| 12/18 | 16.0 | 19.5 | 50 |
| 12/24 | 16.0 | 20.1 | 50 |
| 1/8/55 | 12.1 | 14.5 | 75 |
| 1/14 | 12.8 | 17.9 | 75 |
| 2/11 | 13.2 | 18.6 | 100 |
| 4/2 | 12.1 | 16.2 | 100 |
| 5/14 | 12.6 | 19.9 | 120 |
| 7/9 | 12.0 | 21.4 | 120 |
| 8/20 | 11.2 | 18.6 | 120 |
| 10/8 | 13.7 | 18.3 | 120 |
| 11/4 | 12.3 | 16.0 | 120 |
| 12/18 | 16.0 | 19.5 | 120 |
| 1/29/56 | 13.3 | 19.5 | 120 |
| 2/19 | 12.2 | 18.3 | 75 |
| 2/25 | 12.7 | 18.3 | 120 |

cardial infarction in whom 150 mg. daily did not maintain the prothrombin time at a therapeutic level, and 200 mg. a day had to be given at intervals. However, even though the dose varied from 150 to 200 mg. daily, there was no wide fluctuation in the prothrombin time. Table V also demonstrates the time required for the phenindione to take effect

TABLE V

Short Term Anticoagulant Therapy in Sixty-Two Year Old Man with Myocardial Infarction

| Date | Prothrombin Time (sec.) | | Daily Dose of Phenindione (mg.) |
|---|---|---|---|
| | Control | Patient | |
| 12/10/55, 4:00 P.M. | 13.5 | 11 | 300 |
| 12/11, 8:00 P.M. | 14 | 13.8 | 200 |
| 12/12, 8:00 A.M. | 12.5 | 26 | 150 |
| 12/15 | 14 | 28 | 150 |
| 12/21 | 14 | 24 | 150 |
| 12/24 | 13.5 | 23.5 | 150 |
| 12/27 | 14.5 | 19 | 150 |
| 12/30 | 11 | 26.5 | 200 |
| 1/2/56 | 17 | 29 | 200 |
| 1/4 | 13.5 | 31 | 150 |
| 1/6 | 11 | 27.5 | 200 |
| 1/8 | 13 | 32 | 150 |
| 1/11 | 12 | 27.5 | 150 |
| 1/13 | 14.5 | 31 | 150 |
| 1/14 | 13.8 | 30 | 0 |
| 1/15 | 12.6 | 20.6 | 0 |
| 1/16 | 13.7 | 14.2 | 0 |

TABLE VI

Sensitivity to Small Doses of Phenindione in a Sixty-Five Year Old Man with Myocardial Infarction

| Date | Prothrombin Time (sec.) | | Daily Dose of Phenindione (mg.) |
|---|---|---|---|
| | Control | Patient | |
| 1/12/56 | 13 | 13 | 50 |
| 1/19 | 14 | 30 | 40 |
| 1/26 | 15 | 31.5 | 40 |
| 2/2 | 14.5 | 32.5 | 40 |
| 2/9 | 13.5 | 28 | 40 |
| 3/9 | 14 | 28 | 40 |
| 3/16 | 12 | 32 | 40 |

and the length of time required for this effect to disappear. This patient received the first dose of phenindione at 4:00 P.M. on December 10, 1955 and at 8:00 A.M. on December 12, forty hours later, the prothrombin time was twenty-six seconds, or a little over twice the control. At 8:00 P.M. on January 15, thirty-six hours later, the prothrombin time had dropped to 20.6 seconds, and on January 16, sixty hours after the last dose, it had returned to normal.

Table VI shows the results in a patient sensitive to relatively small doses of phenindione, in contradistinction to the patient in Table V in whom large doses were necessary to maintain the prothrombin time at a therapeutic level. This patient received 50 mg. daily for one week (January 12 to 19, 1956) and at this time the prothrombin time was thirty seconds. The dose was then reduced to 40 mg. daily and the prothrombin time was maintained at two to two and one-half times the control over a period of approximately three months.

Table VII shows that in some instances a thera-

TABLE VII

Phenindione Therapy in Fifty-Six Year Old Man with Myocardial Infarction

| Date | Prothrombin Time (sec.) | | Daily Dose of Phenindione (mg.) |
|---|---|---|---|
| | Control | Patient | |
| 5/5/54 | 13.5 | 14.5 | 300 |
| 5/6 | 13.9 | 17 | 200 |
| 5/7 | 13 | 28 | 100 |
| 5/13 | 13.5 | 32.5 | 100 |
| 5/20 | 13 | 30 | 100 |
| 5/27 | 13.5 | 25 | 125 |
| 6/2 | 14 | 29 | 125 |
| 6/9 | 13.5 | 22.5 | 150 |
| 6/15 | 14 | 31 | 150 |
| 6/19 | 14 | 32 | 150 |
| 6/21 | 13.5 | 33.5 | 150 |

TABLE VIII
Phenindione Therapy in Sixty-Three Year Old Woman with Myocardial Infarction

| Date | Prothrombin Time (sec.) | | Daily Dose of Phenindione (mg.) |
|---|---|---|---|
| | Control | Patient | |
| 3/15 | 14 | 15.5 | 300 |
| 3/16 | 12 | 19 | 100 |
| 3/18 | 14.5 | 26 | 175 |
| 3/20 | 15 | 31 | 150 |
| 3/22 | 14 | 28 | 150 |
| 3/25 | 13.5 | 29 | 150 |
| 3/29 | 14.5 | 35.5 | 150 |
| 4/1 | 14 | 32.5 | 150 |
| 4/8 | 13.5 | 36.5 | 125 |
| 4/13 | 13.5 | 32 | 125 |
| 4/22 | 14.5 | 32 | 125 |
| 5/3 | 13 | 35 | 125 |
| 5/10 | 15 | 33.5 | 125 |

peutic level may be obtained but later the dose has to be increased to maintain this level. This patient with myocardial infarction received 300 mg. on May 5, 1954, 200 mg. on May 6 and then 100 mg. daily; on May 13, the prothrombin time was 32.5 seconds. On May 27, two weeks later, the prothrombin time dropped to twenty-five seconds even though the dose of 100 mg. daily had been continued. The patient was then given 125 mg. of phenindione daily and on June 2, one week later, the prothrombin time was twenty-nine seconds. On June 9, however, even though the dose of 125 mg. daily was continued, the prothrombin time had dropped to 22.5 seconds. He was then given 150 mg. daily and the prothrombin time was maintained at a therapeutic level without further fluctuations.

Table VIII shows the results in a patient whose prothrombin time was maintained at two to two and one-half times the normal. For about two weeks the patient received 150 mg. daily, with the prothrombin time gradually increasing from thirty-one to 36.5 seconds. The phenindione was then reduced to 125 mg. daily and the prothrombin time varied from thirty-five to thirty-two seconds. This is in contradistinction to the data on the patient in Table VII in whom the daily dose had to be increased to maintain the prothrombin time at a therapeutic level.

## Comments

Phenindione (Hedulin) has been administered to a large number of patients without serious complications. Two hundred of these patients were ambulatory, and prothrombin times were determined every one to three weeks. As a rule, they remained constant and did not show wide fluctuations.

Some patients were treated for as long as three years without any untoward effects once the maintenance dose was determined, and with minimal fluctuation in the prothrombin time. Because of the constancy of the prothrombin time after the maintenance dose for the patient had been established, it was not necessary to repeat the test more than once every two to four weeks. Ninety per cent of our ambulatory group had the prothrombin time determined only once every three or four weeks.

In some instances a fairly large dose was necessary to maintain a satisfactory prothrombin level during the first few days of therapy but it then had to be reduced because of the increase in the prothrombin time. Conversely, in a few instances in which the average maintenance dose increased the prothrombin time to an adequate level within a few days, it was necessary to increase the dose to maintain this level.

The dose of phenindione (Hedulin) must be individualized and the prothrombin time should be checked often enough to determine the maintenance dose for each patient. Once the maintenance dose is determined, however, there is very little danger of wide fluctuations in the prothrombin time, whatever the maintenance dose might be. Changes in prothrombin time, when they occur, are usually gradual, affording time for correcting the dose or adopting counter measures if necessary. The number of patients varying from the normal pattern was small, but as with all medications, it is the unusual, unpredictable patient that makes it necessary to observe each one closely to avoid serious reactions.

In patients with a history of bleeding from hemorrhoids, or those who present a history of frequent nosebleeds or similar phenomena, it is possible that anticoagulants may precipitate increased bleeding. Such patients should be observed very closely during anticoagulant therapy. Patients with gastric or duodenal ulcer, ulcerative colitis, and liver or renal disease present an added risk to anticoagulant therapy, particularly if there is a history of previous bleeding.

## Conclusions

1. In our experience, phenindione (Hedulin) was found to be a safe, effective and satisfactory anticoagulant in the prophylaxis and treatment of peripheral vascular disorders and myocardial infarction.

2. When the maintenance dose was established, the prothrombin time did not fluctuate widely and, therefore, it was not necessary to repeat the tests often and administration of the drug could be continued with a great degree of safety.

3. The maintenance dose varied in different individuals, but when established it usually remained constant.

4. The full therapeutic effect was attained within

a short time, and in most instances the prothrombin time returned to normal within forty-eight hours after the medication was omitted.

5. Hemorrhage occurred only twice in our series; once when a patient had a tooth extracted without our knowledge while still receiving the phenindione, and once when a patient inadvertently increased the phenindione to two and one-half times the prescribed dose. When hemorrhage occurs it can be controlled by the omission of the drug and the use of vitamin $K_1$, and the prothrombin time rapidly returns to a normal level.

6. Phenindione was useful in ambulatory as well as hospitalized patients.

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# Management of Thrombophlebitis with Phenylbutazone*

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IT IS my purpose to present a treatment for thrombophlebitis which aborts the clinical syndrome, cuts down on the need for nursing care and hospitalization, and has a potential for lessening the long term complications of venous thrombosis. These objectives are attained through the use of phenylbutazone,† a nonhormonal drug with anti-inflammatory activity of such high order that it rapidly and effectively resolves inflammation in and about the peripheral veins. My experience with 785 patients treated in this way in the five-year period from 1953 to 1958 follows.

At first, only patients with superficial phlebitis were selected, a purely arbitrary move but, as events proved, a fortunate one. Rigid criteria dictated the choice of patient: (1) visible and palpable segments of thrombosed vein had to be present so that not only could the diagnosis bear scrutiny but also the effects of treatment be readily seen and as readily assayed; (2) the phlebitis had to be refractory to traditional treatment. The basic features of such treatment consisted of bedrest with elevation and application of warm soaks to the affected limb, and the addition of combinations of antibiotic and anticoagulant drugs. In several instances ligation of the saphenous and/or superficial femoral veins had been performed to little avail. Incidentally, an ideal control period was thus provided for each patient.

A predictable clinical pattern soon became apparent.[1] The redness, pain and induration so characteristic of acute inflammation in the saphenous veins and their tributaries, and the palpable and visible areas of superficial vein thrombosis began to subside in the first twelve hours. Ambulation was possible with little or no discomfort in most instances by the end of the same day and was encouraged. Bedrest and nursing care were kept to a minimum, and hospitalization was unnecessary except on rare occasions. Only once in the past three years was there a medical reason for the latter.

The degree of improvement was so impressive that soon patients were included in whom the superficial phlebitis was a troublesome complication of a more important underlying condition.[2] These were patients with heart disease, women pregnant and close to term or persons with surgical conditions requiring correction. It was then but a short step to give this drug to all patients and to initiate it at the start of signs and symptoms. Table I shows the results of treatment of the several types of phlebitis.

## RESULTS OF TREATMENT

*Superficial Thrombophlebitis:* A total of 706 patients with superficial thrombophlebitis were observed and treated. Regardless of the varied etiology there was rapid improvement in the vast majority (95 per cent). Emphasis is placed upon the fact that this was achieved by the oral use of 3 gm. (30 tablets) of phenylbutazone in short term treatment of a week or less and that the patient could be managed at home and in the office. Of particular importance is the fact that the patient is spared financial loss by being able to return to work sooner than had been hitherto possible. The conclusion drawn from these studies was that phenylbutazone was an effective type of treatment for superficial thrombophlebitis.

*Thrombophlebitis of Deep Veins:* Needless to say, my experience was not limited to patients with inflammation in the superficial veins alone.

* From the wards and outpatient clinics of the Mount Vernon Hospital, Mount Vernon; Grasslands Hospital, Valhalla; Bronx Municipal Hospital Center, Bronx; and the H.I.P. Medical Group, Montefiore Hospital, Bronx, New York.

† 3,5-Dioxo-1,2-diphenyl-4-pyrazolidine. Manufactured under the trade name Butazolidin® by Geigy Pharmaceuticals, Ardsley, New York.

TABLE I

Results of Treatment in 706 Patients with Superficial Phlebitis (1953 to 1958)

| Type of Phlebitis | No. of Cases | Resolution | |
|---|---|---|---|
| | | Complete | Incomplete |
| In varicose veins | 636 | 623 | 13 |
| Associated with intravenous medication | 16 | 16 | .. |
| Associated with thromboangiitis obliterans | 13 | 13 | .. |
| Associated with malignant disease | 11 | 7 | 4 |
| Associated with pregnancy | 8 | 8 | .. |
| Idiopathic | 17 | 11 | 6 |
| Miscellaneous: Gout, polycythemia, migratory, Mondor's disease | 5 | 5 | .. |
| Total | 706 | 683 (96.7%) | 23 (3.3%) |

Seventy-nine patients with thrombophlebitis of the deep veins in the legs were also treated in the three-year period from 1955 to 1958 (Tables II and III). Most of them (fifty-nine ) had been hospitalized and given anticoagulant drugs for from five to ten days. Phenylbutazone was administered either because of progression of the phlebitis or because there had been little improvement in the clinical picture. Again, quite promptly, within twelve to twenty-four hours there was definite lessening of pain and discomfort, a drop in the body temperature, and softening and lessening of the swelling. This permitted resumption of activity, particularly walking, and shortened the hospital stay appreciably. Instead of the fourteen to twenty-eight days which was the average stay for this disorder in this locality, five to seven days proved sufficient. The remaining twenty patients were not hospitalized either because the phlebitis had been present for more than a week and the optimal time for both hospitalization and anticoagulants had passed, or because this was their expressed wish. These patients were treated only with phenylbutazone and were ambulant from the outset.

The result in thrombophlebitis of deep veins differs from that in superficial veins in that evidence of mechanical blockage of the large venous

TABLE II

Types of Phlebitis of Deep Veins Treated with Phenylbutazone (1955 to 1958)

| Associated Condition | No. of Cases |
|---|---|
| Pregnancy | 14 |
| Postoperative states | 44 |
| Malignant conditions | 3 |
| Idiopathic | 18 |
| Total | 79 |

channels is present in the peripheral edema noted when the patient has been up and about. Such swelling is readily controllable by elastic compression and in my patients has proved to be neither massive nor troublesome. The basis for this may very well be the small shrunken or porous clot which I have observed in animals treated with phenylbutazone[3] and more recently in human experiments. Histologically this is the type of venous thrombosis in which complete obstruction of the vein is not likely and the possibility for recanalization is good. The combination of anticoagulants to combat thromboembolism and phenylbutazone to treat the clinical picture seems to be an optimal one from the theoretic aspect, and a further report will follow.

## Comments

In a discussion of the ideal treatment for an illness one looks for specificity and rapid effect upon the disease process, for facility and ease of administration, for a minimum of side effects and toxic reactions, and for economic savings for the patient.

The specific, prompt and effective action of phenylbutazone upon thrombophlebitis of the

TABLE III

Results of Treatment in Seventy-nine Patients with Phlebitis of Deep Veins (1955 to 1958)

| Region Involved | No. of Cases | Resolution | |
|---|---|---|---|
| | | Complete | Incomplete |
| Iliofemoral | 59 | 57 | 2 |
| Popliteal | 16 | 16 | .. |
| Veins of foot | 3 | 2 | 1 |
| Axillary | 1 | 1 | .. |
| Total | 79 | 76 (96.2%) | 3 (3.8%) |

superficial or deep veins of the extremities has been reproduced and reported in numerous controlled studies in this country and abroad.[4–12] The simplicity and ease of application are obvious and need no further comment.

It is economical in terms of time, money and materials. The management of this ubiquitous disorder has become an office or home type of treatment in approximately 500 patients in my series. This saves the hospital bed, already scarce and costly, for patients with more serious illnesses. It eliminates nursing care and time-consuming procedures such as warm soaks and hot pads. The patient's financial loss is kept at a minimum because he returns to work as soon as relief from pain permits—a matter of several days instead of being confined to bed at home or in the hospital for many weeks.

*Complications and Side Effects:* It is a safe treatment when used intelligently. The complications I have seen have been minor and reversible: (1) dyspepsia and heartburn, thirty-nine patients (5 per cent) (this can be relieved and prevented by concomitant use of antacids); (2) skin eruptions, four patients (0.5 per cent); and (3) generalized edema, four patients (0.5 per cent).

In the treatment of 785 patients, I have not encountered a single instance of the graver complications which have appeared in the literature,[13] such as granulocytopenia, hepatic involvement, gastrointestinal bleeding or thromboembolism. In part this has been due to a basic feature—this is short term treatment and such complications are more frequently seen after the first week of therapy. On the other hand, it does not seem warranted to expect 100 per cent freedom from side effects or complications with this or any of the other potent drugs such as the corticosteroids, the antibiotics or tranquilizers which are meant for specific use.

## Conclusions

In summary, the use of phenylbutazone in acute thrombophlebitis is a distinct step in the proper direction. The management of the superficial variety has been greatly simplified and can be carried out as a routine procedure in the doctor's office. Phenylbutazone alone can and should be used in recommended dosage usually for one week to control the majority of cases.

Phlebitis of the deep veins responds equally as well but elastic compression is necessary to control the swelling which is seen when the patient is up and about. Anticoagulants should be used in conjunction with phenylbutazone in recent cases of phlebitis of the deep veins. Together, the two drugs, which have their own spheres of action, appear to be synergistic in effect.

Finally, in the treatment of acute thrombophlebitis, the benefits derived from the use of phenylbutazone far outweigh the reasonable incidence of transient side effects which have been encountered.

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# Review

# Combined Mitral and Aortic Stenosis

## Clinical and Physiologic Features and Results of Surgery*

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COMBINED rheumatic mitral and aortic stenosis is not a rare disease despite the lack of frequent descriptive reports in the medical literature.

The present review reports the clinical and hemodynamic findings in patients with this disease in whom obstruction was proved to be the major issue at each valve. The results of the surgical treatment will be presented and the criteria for selection for surgery outlined.

### MATERIAL

The series consists of 141 patients treated surgically during the interval from April 1953 to May 1958 (Table I). There were fifty-two males and eighty-nine females who had mitral and aortic stenosis alone (group 1) or in combination with adynamic, physiologically insignificant, aortic regurgitation or mitral regurgitation (group 2). Their ages ranged from twenty-three to sixty-seven years. One-third were in the forty to fifty year-age group.

### CLINICAL MANIFESTATIONS

The clinical findings are summarized in Table II. A previous history of rheumatic fever was obtained in seventy-four cases. The natural history of the disease then followed an unpredictable course with variable features that characterize aortic and mitral stenosis when seen independently.

*Dyspnea* and *fatigue* were frequent as initial disturbances and were observed in 93.6 and 86.5 per cent of cases, respectively. The degree of dyspnea and the intensity of the muscular fatigue varied over a wide range. In general, the severity of the shortness of breath and weakness paralleled the total duration of cardiac disability and was influenced by the general form of the medical regimen and the work load assumed by the patient. The mean duration of time of these two symptoms prior to study by us did exceed that of a comparable group of cases of aortic stenosis.[1] The frequency of nocturnal dyspnea was higher in the combined group.

*Edema* was present in 63.0 per cent. Changes within the pulmonary circuit secondary to mitral stenosis played a role in some cases. It was invariably a later manifestation of cardiac decompensation although its presence did not necessarily indicate a far advanced state of rheumatic heart disease.

*Hemoptysis* was present in 42 per cent while 20 per cent had *emboli* to either the brain, lung or the extremities.

*Angina*, *vertigo* and *syncope* occurred in less than 25 per cent of the patients and were rarely encountered in patients with small hearts. These three symptoms were less prevalent than in those with pure aortic stenosis where true coronary pain occurs in half the cases and syncope or vertigo in nearly one-third. The various influences responsible for this change have been suggested in another report.[2]

Nearly half of the patients had *atrial fibrillation* while a normal sinus rhythm was present in the rest. *Blood pressure* levels were within the normal range.

*Auscultation Findings:* On cardiac auscultation the aortic second sound was diminished or absent in the majority and normal in intensity in 22.4 per cent. A rough systolic murmur in the aortic area was present in all patients with typical radiation to the neck and apex. An early blowing diastolic murmur of aortic regurgitation was present along the left sternal border in 68 per cent. Leak at the aortic valve was not considered dynamic because of

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TABLE I
Diagnosis and Patient Material

| Group | Diagnosis | Patients (no.) | Male | Female | Operative Approach | | |
|---|---|---|---|---|---|---|---|
| | | | | | Transaortic Aortic Commissurotomy and Right Mitral Commissurotomy | Transventricular Aortic Commissurotomy and Left Mitral Commissurotomy | Open Heart |
| 1 | AS MS | 36 | 9 | 27 | 4 | 28 | 3 |
| 2 | AS MS ai mi | 105 | 43 | 62 | 20 | 80 | 6 |
| Totals | | 141 | 52 | 89 | 24 | 108 | 9 |

NOTE: AS = aortic stenosis. MS = mitral stenosis. ai = insignificant aortic insufficiency. mi = insignificant mitral insufficiency.

the lack of a wide pulse pressure and low diastolic blood pressure, and the absence of all the characteristic peripheral signs of aortic regurgitation.

The intensity of the basal murmurs was such that the rough mid-late diastolic murmur of mitral stenosis was oftentimes difficult to identify. In many it was well localized and in 3 per cent it could not be heard at all. Uncertainty also developed when the murmur of aortic regurgitation was transmitted to the apex although its higher pitch and immediate occurrence after the second sound permitted separation in all but a few.

The mitral first sound was less sharp than in isolated mitral stenosis and its frequency characteristics tended to be obscured by the rough murmur of aortic stenosis transmitted from the base. In doubtful cases, exercise increased the snapping quality of the first sound.

*Mitral Regurgitation:* In 19 per cent, mitral regurgitation of minor degree was encountered at surgery (it was based on a range of 0 to 4 plus). In this group, the apical systolic murmur was generally less rough and more blowing. When doubt existed in regard to the significance of the apical systolic murmur, a cardiac ventriculogram was performed with direct injection of radiopaque material into the left ventricle.[3] In the absence of dynamic mitral regurgitation, there was no opacification of the left atrium.[4]

Finally, in 3 per cent, the diagnosis of mitral valve disease was suspected because of the presence of either atrial fibrillation, left atrial enlargement or a sharp mitral first sound and confirmed by catheterization of the left heart.

*Electrocardiographic Findings:* A standard 12 lead electrocardiogram was performed in all cases (Table II). Right ventricular hypertrophy was present in 15 per cent while a slightly larger group (18.4 per cent) demonstrated a pattern of left ventricular hypertrophy. Combined ventricular hypertrophy was present in nearly 4 per cent. Conduction defects were not uncommon, but abnormal coronary patterns, as expected, were rare. The most frequent abnormality was atrial fibrillation and it was present in 46.8 per cent of the total group.

*X-ray Findings:* A review of the cardiac roentgenograms revealed that all but four patients had an

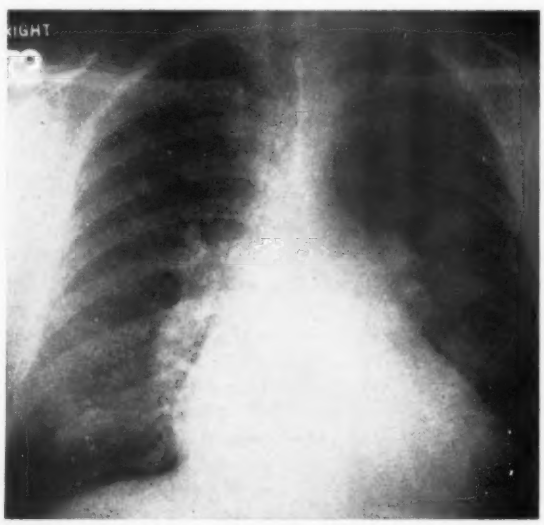

FIG. 1. Chest roentgenogram in a patient with combined mitral and aortic stenosis. There is usually x-ray evidence of enlargement of both ventricular chambers, the pulmonary segment, and the left atrium. However, the cardiac configuration can vary from typical mitral to typical aortic.

TABLE II
Clinical Manifestations

| Manifestation | Group 1 | Group 2 | Total Patients (no.) | Combined Incidence (%) |
|---|---|---|---|---|
| Dyspnea | 34 | 98 | 132 | 93.6 |
| Fatigue | 32 | 90 | 122 | 86.5 |
| Edema | 17 | 68 | 85 | 63 |
| Atrial fibrillation | 19 | 47 | 66 | 47 |
| Hemoptysis | 13 | 32 | 45 | 32 |
| Paroxysmal nocturnal dyspnea | 11 | 40 | 51 | 36 |
| Angina | 7 | 25 | 32 | 23 |
| Vertigo | 10 | 25 | 35 | 25 |
| Emboli | 8 | 19 | 27 | 20 |
| Syncope | 6 | 16 | 22 | 15.6 |
| Normal aortic 2nd sound | 12 | 21 | 33 | 22.4 |
| Heart size | | | | |
| Normal | 2 | 2 | 4 | 2.8 |
| 1 plus | 4 | 14 | 18 | 72.8 |
| 2 plus or more | 30 | 89 | 119 | 84.4 |
| Electrocardiogram | | | | |
| Normal | 6 | 13 | 19 | 13.4 |
| Left ventricular hypertrophy | 7 | 19 | 26 | 18.4 |
| Right ventricular hypertrophy | 5 | 16 | 21 | 15 |
| Combined ventricular hypertrophy | 2 | 3 | 5 | 3.5 |
| Heart block | 7 | 3 | 10 | 7 |
| Coronary patterns | 0 | 4 | 4 | 3 |
| Auricular fibrillation | 19 | 47 | 66 | 46.8 |
| Normal sinus rhythm | 17 | 58 | 75 | 53.2 |

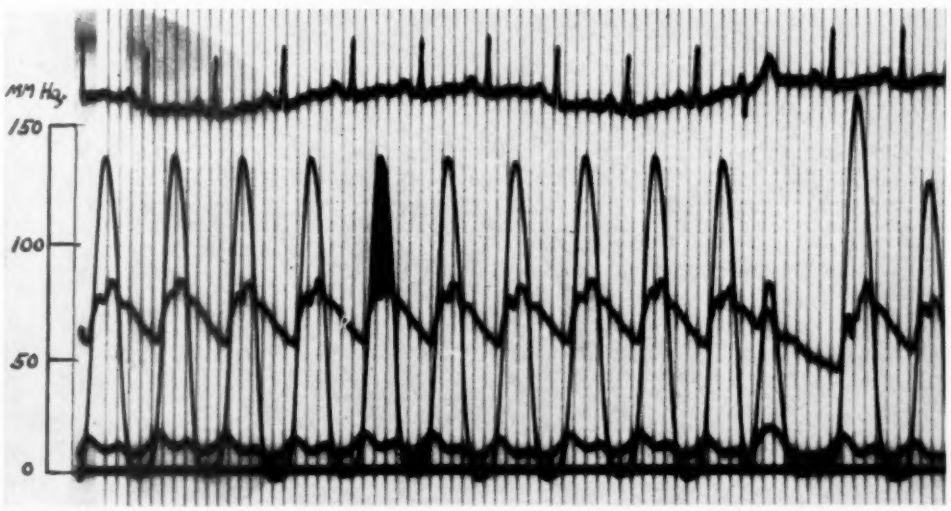


FIG. 2. Left heart catheterization tracings in a patient with combined mitral and aortic stenosis. Left atrial and left ventricular and aortic tracings recorded simultaneously. Top shaded area in the fifth cycle represents the systolic ejection gradient (50 mm. Hg) while bottom shaded area represents ventricular filling gradient (9 mm. Hg). Both are significantly elevated. Electrocardiogram above.

increase in heart size (Table II). In 84.4 per cent of the entire series, it was estimated at greater than 2 plus (range 0 to 4 plus). Contours varied but most had enlargement of the pulmonary artery or outflow tract of the right ventricle (Fig. 1). Left atrial enlargement was constantly observed although, in the presence of significant left ventricular enlargement, it had to be differentiated from the left atrial dilatation that is seen in patients subjected to bouts of left heart failure.

TABLE III
Left Heart Catheterization Data

| Case | Age (yr.) | Rhythm | Time of Study | Date | Pressure (mm. Hg) | | | Ventricular Filling Gradient (mm. Hg) | Ventricular Systolic Ejection Gradient (mm. Hg) |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | Left Atrium (mean) | Left Ventricular | Brachial Artery | | |
| E. R. | 46 | N. S. R. | Preop. | 11/29/55 | (18) | 145/8 | 130/70 (94) | 9 | 25 |
| | | N. S. R. | Postop. | 9/10/56 | (6) | 131/7 | 120/44 (82) | 6 | 11 |
| J. S. | 35 | N. S. R. | Preop. | 12/6/55 | (30) | 140/20 | 124/72 (86) | 20 | 16 |
| | | N. S. R. | Postop. | 12/16/55 | (29) | 126/6 | 110/64 (80) | 14 | 16 |
| S. D. | 42 | A. F. | Preop. | 9/13/56 | (30) | 120–195/7 | 105–152/85 (109) | 22 | 43 |
| | | A. F. | Postop. | 10/1/56 | (16) | 145–188/5–10 | 105–122/65–55 (81) | 8 | 40<br>56 |
| M. F. | 40 | A. F. | Preop. | 12/12/56 | (25) | 180–200/5 | 100/65 (76) | 16 | 80<br>100 |
| | | N. S. R. | Postop. | 1/2/57 | (13) | 101/5 | 100/60 (74) | 5 | 1 |
| R. M. | 44 | N. S. R. | Preop. | 1/28/57 | (8) | 120/−5 | 97/53 (74) | 14 | 23 |
| | | A. F. | Postop. | 2/14/57 | (3) | 128–130/−1 −1 | 111-112/56 58 | 7 | 17<br>18 |
| P. D. | 33 | A. F. | Preop. | 10/13/55 | (34) | 161/13 | 119/76 (94) | 17.6 | 42 |
| D. M. | 36 | N. S. R. | Preop. | 12/8/55 | (12) | 160/4 | 106/66 (82) | 8 | 54 |
| G. M. | 57 | A. F. | Preop. | 5/10/56 | (19) | 190–140/12–2 | 160–136/76–84 (103) | 9 | 30 |
| B. B. | 37 | A. F. | Preop. | 9/18/56 | (17) | 160–200/10 | 110–119/73 (79) | 10 | 40–81 |

## Cardiac Catheterization

Combined heart catheterization was carried out in eight patients and left heart catheterization alone in an additional twenty-three by technics previously described[5,6] (Tables III and IV).

### METHODS

The cardiac output was calculated by the direct Fick method. Blood oxygen was determined by the method of Van Slyke and Neill.[7] The respiratory gases were determined by the Pauling oxygen analyzer. The zero line was taken at 5 cm. below the angle of Louis. Pressure gradients were calculated by planimetric integration. Valve areas, pulmonary resistance and ventricular work were calculated by modification of the formulas of Gorlin and Gorlin.[8]

### RESULTS

The *cardiac index* was below normal in all patients and averaged 1.8 L. per minute per square meter of body surface area.

The *left atrial pressure* was elevated in most patients and averaged 21.6 mm. Hg, with a range of 8 to 35 mm. Hg. It was slightly higher in patients with atrial fibrillation. The pulmonary venous capillary pressures and those of the left atrium were quite comparable.

TABLE III (*Continued*)

| Case | Age (yr.) | Rhythm | Time of Study | Date | Pressure (mm. Hg) | | | Ventricular Filling Gradient (mm. Hg) | Ventricular Systolic Ejection Gradient (mm. Hg) |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | Left Atrium (mean) | Left Ventricular | Brachial Artery | | |
| E. Mc. | 39 | N. S. R. | Preop. | 10/24/56 | (11) | 180/2 | 136/62 (95) | 10 | 44 |
| R. R. | 55 | A. F. | Preop. | 3/4/57 | (17) | 140–210/8–12 | 120–180/80–92 (105) | 7 | 20–30 |
| H. K. | 38 | A. F. | Preop. | 3/28/57 | (20) | 100–142/1 – 6 | 98–130/86– 72 | 21 | 12 |
| M. R. | 47 | A. F. | Preop. | 4/8/57 | (20) | 140–255/3 – 16 | 118–165/88– 52 (94) | 12 | 22–90 |
| V. O. | 40 | A. F. | Preop. | 3/22/57 | (15) | 207–148/16– 7 | 133–108/68– 76 (95) | 8 | 40–74 |
| T. C. | 35 | N. S. R. | Preop. | 5/6/57 | (12) | 164/7 | 127/58 (80) | 8.5 | 37 |
| J. G. | 56 | A. F. | Preop. | 12/3/57 | (22) | 120–234/9– 11 | 100–180/75–103 (115) | 19 | 20–54 |
| J. L. | 47 | A. F. | Preop. | 10/13/57 | (16) | 150–210/10– 11 | 90–120/55– 60 (68) | 11.6 | 60–90 |
| G. B. | 41 | A. F. | Preop. | 3/20/58 | (23) | 110–165/4 – 20 | 95–143/52– 75 (92) | 16 | 15–23 |
| M. M. | 48 | N. S. R. | Preop. | 4/6/58 | (20) | 230–262/4 – 5 | 102–104/55– 65 (77) | 9.1 | 128–158 |
| H. E. | 44 | N. S. R. | Preop. | 11/30/57 | (35) | 153/17 | 114/65 | 18 | 40 |
| M. L. | 29 | N. S. R. | Preop. | 5/7/57 | (32) | 119/8 | 81/64 | 27 | 38 |
| E. M. R. | 44 | A. F. | Preop. | 1/3/58 | (24) | 120–178/8–19 | 110–150/68– 80 (85) | 10–28 | 11 |
| R. C. | 35 | N. S. R. | Preop. | 12/20/57 | (21) | 175/1 | 108/69 (94) | 15 | 67 |

A *pressure gradient across the mitral valve* during ventricular filling was noted in every patient (Fig. 2). It averaged 13.3 mm. Hg with a range of 5 to 27 mm. Hg. In seventeen patients, it was greater than 10 mm. Hg. The *mitral valve flow* was reduced in all and ranged from 58 to 174 ml./V.F.P. second. The *mitral valve areas* ranged from 0.6 to 1.7 cm.$^2$ The average area was 1.12 cm.$^2$

*Pulmonary artery mean pressure* ranged from 25 to 32 mm. Hg. Markedly elevated mean pulmonary artery pressures (40 mm. Hg or higher) were not observed in these patients. The *pulmonary vascular resistance* was normal in two patients and mildly to moderately elevated in the rest. It ranged from 114 to 463 dynes sec. cm.$^{-5}$

*Right ventricular work* was not increased in any patient and ranged from 0.43 to 0.99 kg. per minute.

The *aortic valve flow* was reduced in all but one patient, ranging from 70 to 208 cc. per systolic ejection second, and averaging 110.9 cc.

The *systolic ejection pressure in the left ventricle* was elevated in all but eight with a range of 110

TABLE
Combined Heart

| Patient | $O_2$ Consumption (ml./min./$M^2$) | A-V Difference (vol. %) | Cardiac Output (L./min.) | Cardiac Index (L./min./$M^2$) | Heart Rate (beats/min.) | Pressure (mm. Hg) | | | | | | | Ventricular Filling Period (sec.) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Right Atrium (mean) | Right Ventricle | Pulmonary Artery | Left Atrium (mean) | Left Ventricle | Aorta | Brachial Artery | |
| M. P. | 213 | 7.1 | 3.0 | 1.7 | 80 | (10) | 39/4 | 39/22 (32) | 19 | 153/8 | 116/82 (96) | ... | 0.35 |
| R. N. | 163 | 4.7 | 3.5 | 2.3 | 109 | (2) | 50/14 | 50/25 (30) | 25 | 122/5 | ... | 110/60 (96) | 0.22 |
| N. C. | 159 | 8.5 | 1.9 | 1.0 | 92 | 5 | 40/6 | 40/20 (30) | 19 | 200/10 | ... | 120/84 (88) | 0.30 |
| C. P. | 193 | 5.5 | 3.5 | 2.2 | 102 | 0 | 40/0 | 40/20 (25) | 20 | 200/10 | 90/60 (80) | 120/60 (90) | 0.24 |
| H. P. | 155 | 7.0 | 2.2 | 1.4 | 64 | 10 | 48/9 | 48/20 (30) | 20 | 239/12 | ... | 107/53 (74) | 0.44 |
| W. M. | 206 | 5.3 | 3.9 | 2.5 | 85 | 10 | 43/0 | 45/20 (25) | 9 | 143/5 | 96/60 (65) | 124/75 (100) | 0.52 |
| H. P. | 154.9 | 7.0 | 2.2 | 1.4 | 64 | (10) | 48/9 | 48/20 (30) | 20 | 239/12 | ... | 107/53 (79) | 0.44 |
| R. H.* | ... | ... | 4.4 | 2.3 | 117 | ... | ... | ... | (17) | 235/6 | ... | 145/77 (95) | 0.22 |

NOTE: V.F.P. = ventricular filling period. S.E.P. = systolic ejection period.
* Cardiac output was performed by dye technic hence right heart data were not obtained.

to 255 mm. Hg. The *end diastolic pressure* in the left ventricle was frequently elevated. A *systolic ejection gradient* was constantly observed across the aortic valve, ranging from 16 to 158 mm. Hg. It averaged 49.8 mm. Hg in the total group. The brachial artery pressure was used for this determination in all in whom the central aortic pressure could not be obtained. In five patients, in whom both measurements were available, the brachial artery pressure was higher.

The *aortic valve areas* were critically reduced, ranging from 0.2 $cm.^2$ to 1.7 $cm.^2$ The average area was 0.57 $cm.^2$

The *total work of the left ventricle* was increased in three patients. The average was 3.75 kg.M./minute which is just at the upper range of normal. (Normal range is 2.9 to 3.9 kg.M./minute.)

## Surgical Treatment

The surgical principles concerned with the management of combined aortic and mitral stenosis have been previously detailed.[9] Three acceptable technics are now available for elimination of the mechanical impediment at the mitral and aortic valve at a single operation. One involves the performance of a mitral commissurotomy via the common pathway of the left atrial appendage (left-sided approach) with a transventricular attack on the aortic valve. Another method utilizes the transaortic technic to correct the structural abnormalities of the aortic valve while the mitral commissures are separated after entrance into the left atrial chamber by way of the interatrial groove (right-sided approach). More recently direct vision surgery has been carried out in some of the valvular defects of this type by shunting blood from the venae cavae to the femoral or subclavian artery with the aid of a heart-lung apparatus. This provides the surgeon with a relatively dry field for operation.

### OPERATIVE MORTALITY

The operative mortality for the entire series was 19.2 per cent (Table V). It was 17.5 per cent when the transventricular approach to the aortic valve was employed and 8.3 per cent when a transaortic aortic commissurotomy was used. There were only two deaths in the group of thirty-three patients with pure obstructive lesions of the aortic and mitral valves in whom closed surgery was performed. A higher mor-

IV
Catheterization Data

| Left Ventricular Filling Gradient (mm. Hg) | Mitral Valve Flow (ml./ V. F. P. sec.) | Mitral Valve Area (cm.²) | Systolic Ejection Period (sec.) | Aortic Gradient (mm. Hg) | Aortic Valve Flow (cc./ S. E. P. sec.) | Aortic Valve Area (cm.²) | Left Ventricular Mean Systolic Pressure (mm. Hg) | Pulmonary Vascular Resistance (dynes sec. cm.$^{-5}$) | Right Ventricular Work (kg. m./ min.) | Left Ventricular Work (kg. m./ min.) | Total left Ventricular Work (kg. m./ min.) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 10 | 105 | 1.1 | 0.27 | 35 | 139 | 0.5 | 121 | 348 | 0.79 | 2.34 | 2.96 |
| 11 | 146 | 1.4 | 0.24 | 17 | 153 | 0.9 | 117 | 114 | 0.99 | 3.16 | 3.86 |
| 7 | 70 | 0.9 | 0.30 | 102 | 70 | 0.2 | 164 | 463 | 0.43 | 1.26 | 2.36 |
| 13 | 134 | 1.1 | 0.2 | 66 | 150 | 0.4 | 175 | 114 | 0.79 | 2.85 | 5.54 |
| 12 | 58 | 0.8 | 0.39 | 124 | 90 | 0.2 | 176 | 363 | 0.60 | 1.49 | 3.54 |
| 5 | 89 | 1.7 | 0.22 | 17 | 208 | 1.7 | 118 | 288 | 0.90 | 3.60 | 4.24 |
| 11.6 | 58 | 0.6 | 0.39 | 132 | 89.5 | 0.2 | ... | 369 | 0.603 | 1.587 | ... |
| 16 | 174 | 1.6 | 0.20 | 90 | 188 | 0.46 | ... | ... | ... | 3.146 | ... |

tality rate (66 per cent) was experienced with the open heart technic, and all three patients with pure aortic and mitral stenosis succumbed.

The immediate causes of death are listed in Table VI. Ventricular fibrillation and technical accidents were responsible for most of the fatalities during or immediately after combined commissurotomy.

POSTOPERATIVE HOSPITAL COURSE

Cardiac complications without mortality developed in approximately one-third of the cases (Table VII). They were more common in the group operated on by the transventricular approach and consisted of transient bouts of congestive failure (14 per cent), cardiac arrhythmias (12.7 per cent), and vascular accidents (3.6 per cent). In one patient subacute bacterial endocarditis developed due to staphylococcus.

The usual postthoracotomy complications of chest pain, retained secretion and pleural effusions were encountered.

TABLE V
Operative Mortality

| Group | Patients (no.) | Operative Approach | | | | | | Combined Mortality (%) |
|---|---|---|---|---|---|---|---|---|
| | | Transventricular Aortic Commissurotomy and Left Mitral Commissurotomy | | Transaortic Aortic Commissurotomy and Right Mitral Commissurotomy | | Open Heart | | |
| | | Patients (no.) | Deaths | Patients (no.) | Deaths | Patients (no.) | Deaths | |
| 1 | 36 | 28 | 2 | 5 | 0 | 3 | 3 | |
| 2 | 105 | 80 | 17 | 19 | 2 | 6 | 3 | |
| Totals | 141 | 108 | 19 (17.5%) | 24 | 2 (8.3%) | 9 | 6 (66.6%) | 19.2% |

TABLE VI
Causes of Postoperative Death

| Causes | Transventricular Aortic Commissurotomy and Left Mitral Commissurotomy | Transaortic Aortic Commissurotomy and Right Mitral Commissurotomy | Open Heart |
|---|---|---|---|
| Ventricular fibrillation | 9 | 2 | 4 |
| Technical accidents | 5 | 0 | 0 |
| Cerebral emboli | 2 | 0 | 1 |
| Transfusion reaction | 1 | 0 | 0 |
| Acute renal shut-down | 1 | 0 | 1 |
| Subacute bacterial endocarditis | 1 | 0 | 0 |

Miscellaneous complications included one case each of psychosis, transfusion reaction and wound hemorrhage. The two patients who survived open heart surgery had no serious postoperative cardiac complications.

FOLLOW-UP REVIEW

The postoperative review was limited to patients operated upon at least six months previously and included a total of eighty-two individuals (Table VIII). Slightly more than 59 per cent were followed for a period of two years or more. Late deaths, symptomatic improvement, late complications and alterations in objective manifestations are considered separately. Because of the small series and short follow-ups, the open cases are not included.

TABLE VIII
Duration of Follow-Up Review

| Months Since Surgery | Patients (no.) |
|---|---|
| 0–6 | 2 |
| 7–12 | 5 |
| 13–18 | 13 |
| 19–24 | 13 |
| 25–36 | 15 |
| 37–48 | 20 |
| 49–60 | 12 |
| 61–69 | 2 |

*Late Deaths and Complications:* There were nine late deaths following discharge from the hospital. The intervals from surgery to death are listed in Table IX.

*Heart failure* was the chief cause of death although one patient succumbed to subacute bacterial endocarditis five months after surgery and another to mesenteric embolism twenty-two months after combined commissurotomy.

Eleven patients experienced *cerebral vascular accidents* without residuum. Only one patient was left with a persistent hemiplegia and partial aphasia. There were seven patients with *peripheral emboli* handled successfully either by conservative management utilizing anticoagulants or by direct embolectomy. Three other patients gave a history suggestive of embolization.

*Symptomatology:* In the surviving patients of the follow-up group, inquiry was made into their ability to perform exactly the same type

TABLE VII
Postoperative Hospital Complications

| | Group 1 | | Group 2 | |
|---|---|---|---|---|
| | Transventricular Aortic Commissurotomy and Left Mitral Commissurotomy | Transaortic Aortic Commissurotomy and Right Mitral Commissurotomy | Transventricular Aortic Commissurotomy and Left Mitral Commissurotomy | Transaortic Aortic Commissurotomy and Right Mitral Commissurotomy |
| Rheumatic fever | 1 | ... | 1 | ... |
| Congestive heart failure | 11 | ... | 5 | ... |
| Subacute bacterial endocarditis | 0 | ... | ... | 1 |
| Atrial fibrillation (converted) | 1 | ... | 7 | 1 |
| Atrial fibrillation (permanent) | 1 | ... | 3 | 1 |
| Cerebral emboli | ... | ... | 1 | 2 |
| Visceral emboli | ... | ... | 1 | ... |

TABLE IX
Late Deaths Following Surgery

| Cause of Death | Group 1 | | Group 2 | |
|---|---|---|---|---|
| | Transventricular Aortic Commissurotomy and Left Mitral Commissurotomy | Transaortic Aortic Commissurotomy and Right Mitral Commissurotomy | Transventricular Aortic Commissurotomy and Left Mitral Commissurotomy | Transaortic Aortic Commissurotomy and Right Mitral Commissurotomy |
| Heart failure | 2 {29 mo., 18 mo.} | ... | 3 {10 mo., 36 mo., 4 mo.} | 1 (10 mo.) |
| Subacute bacterial endocarditis | ... | ... | | 1 (3 mo.) |
| Mesenteric embolism | ... | ... | 1 (22 mo.) | |
| Unknown cause | ... | ... | 1 (29 mo.) | |

of activity which previously had led to the development of clear-cut cardiac symptoms. This type of analysis revealed that 86.4 per cent of the living patients were clinically improved, 10.9 per cent were unchanged and two patients were worse (Table X), excluding the open cases.

TABLE X
Change in Functional Class Following Surgery

| | Same | Better | Worse |
|---|---|---|---|
| Transventricular aortic commissurotomy and left mitral commissurotomy | 6 | 51 | 1 |
| Transventricular aortic commissurotomy and right mitral commissurotomy | 2 | 12 | 1 |
| Open aortic commissurotomy and mitral commissurotomy | 0 | 2 | 0 |
| Totals | 8 | 65 | 2 |

All but one in the follow-up group experienced *dyspnea* preoperatively and over 84.7 per cent were distinctly improved by combined commissurotomy. The change occurred in some almost immediately (Tables XI and XII).

*Fatigue*, present in all but six cases prior to surgery, disappeared or became less of a problem in 76.1 per cent. A slightly smaller group was relieved of *edema* while the improvement in nocturnal dyspnea and vertigo proved to be striking (Tables XI and XII).

*Hemoptysis* recurred in only one of the twenty-one patients who experienced it preoperatively, while *angina* improved in all but two of the original nineteen.

*Objective Manifestations:* The classic auscultatory findings of aortic stenosis and mitral stenosis, alone, or combined with insignificant degrees of regurgitation, were unchanged in 39 per cent of the cases.

In 27 per cent the *mitral first sound* became less

TABLE XI
Effect of Combined Mitral and Transventricular Aortic Commissurotomy on Clinical Manifestations

| Manifestation | Present Preoperatively | Postoperative Status | | | |
|---|---|---|---|---|---|
| | | Absent | Improved | Same | Worse |
| Dyspnea | 56 | 7 | 39 | 8 | 2 |
| Fatigue | 55 | 6 | 45 | 12 | 2 |
| Edema | 39 | 12 | 10 | 16 | 1 |
| Paroxysmal nocturnal dyspnea | 16 | 13 | 0 | 2 | 1 |
| Vertigo | 13 | 10 | 1 | 2 | 0 |
| Hemoptysis | 11 | 10 | 0 | 1 | 0 |
| Angina | 10 | 8 | 1 | 0 | 1 |
| Syncope | 8 | 8 | 0 | 0 | 0 |
| Emboli | 4 | 3 | 0 | 1 | 0 |

TABLE XII
Effect of Combined Mitral and Transaortic Commissurotomy on Clinical Manifestations

| Manifestation | Present Preoperatively | Postoperative Status | | | |
|---|---|---|---|---|---|
| | | Absent | Improved | Same | Worse |
| Dyspnea | 16 | 3 | 12 | 1 | .. |
| Fatigue | 12 | 2 | 8 | 1 | 1 |
| Vertigo | 11 | 11 | .. | .. | .. |
| Hemoptysis | 10 | 10 | .. | .. | .. |
| Paroxysmal nocturnal dyspnea | 10 | 9 | .. | .. | 1 |
| Edema | 9 | .. | 8 | .. | 1 |
| Angina | 9 | .. | 8 | .. | 1 |
| Syncope | 1 | 1 | .. | .. | .. |
| Emboli | 0 | .. | .. | .. | .. |

sharp or normal. This alteration occurred much more commonly when the mitral commissurotomy was carried out by the standard right-sided approach. Changes in the intensity of the *apical systolic murmur*, when it was noted preoperatively, were unimpressive. In a few cases an apical systolic murmur appeared when it had not been noted before surgery. In none of these was the regurgitation considered of dynamic significance. In approximately one of every eleven patients, the *rough diastolic murmur* of mitral stenosis appeared for the first time after surgery or was increased in intensity.

Changes in the auscultatory events at the base of the heart were less impressive. In only 7.8 per cent of the cases was a significant decrease in the intensity of the *aortic systolic murmur* thought to be present. Some of these were associated with an increase in loudness of the aortic second sound. In only three patients did a loud, early *blowing diastolic murmur* develop along the left sternal border. In some an increase in intensity of the aortic regurgitation murmur occurred following commissurotomy. However, there were no changes in the mean blood pressure values, and dynamic aortic regurgitation was not produced in a single case.

No constant or convincing changes in the *roentgenographic or electrocardiographic patterns* were noted, even when the observations were made as long as two years after the definitive surgery. Dramatic alterations, although demonstrated in an exceptional case, were most unusual and represented the exception rather than the rule.

*Left heart catheterization* was repeated postoperatively in five cases (Table III). Preoperatively, the mean gradient during ventricular filling across the mitral valve averaged 16 mm. Hg while postoperatively it measured 7.9 mm. Hg in this group. The mean left atrial pressure fell by 40 per cent.

The mean pressure gradient across the aortic valve during systolic ejection was 49 mm. Hg (in two cases the central aortic pressure was obtained while in others the brachial artery pressure was used in the calculation). Postoperatively, the mean pressure gradient measured 16 mm. Hg. However, in one patient no actual change in gradients was recorded. No consistent change was noted in systolic ejection pressure or in left ventricular diastolic pressure following combined commissurotomy.

## Comments

### Clinical and hemodynamic findings compared to those in pure mitral stenosis or pure aortic stenosis

*Symptoms:* Marked commissural fusion at both the mitral and aortic valves produces a typical spectrum of disturbances. Of every ten cases in our series, it was responsible for dyspnea and fatigue in nine; edema in six; hemoptysis in three; and vertigo, angina or syncope in two.

The symptom complex of dyspnea, fatigue and emboli varies little in incidence as compared to what is encountered in isolated mitral stenosis.[10] The sex is predominately female as in pure mitral valve obstruction.

The triad of syncope or vertigo, angina or nocturnal dyspnea was comparable to the frequency reported in isolated aortic stenosis.[1]

*Physical Signs:* The auscultatory features of this disease are dominated by the murmurs produced by the aortic valve obstruction. The rough systolic murmur of aortic stenosis was widely transmitted and is associated with a

diminished or absent aortic second sound in nearly eight of ten. The murmur of mitral stenosis tends to be more isolated.

Inspection and palpation of the anterior chest frequently revealed two types of pulsations. A left lower parasternal and epigastric lift was generally combined with a forceful and sustained hypertrophy.

*X-ray and Electrocardiographic Findings:* Various contours are noted on the roentgenograms. In some the configuration is classically that of right ventricular hypertrophy with prominence of the pulmonary artery segment. Some show evidence of left ventricular dilatation or hypertrophy with enlargement of the ascending aorta. In eight of ten, moderate to marked cardiac enlargement is present.

The electrocardiograms revealed a pattern of right, left or combined ventricular hypertrophy in four of ten. Many of the "normal group" are thought to be cases in which the electrical forces from each of the two ventricles balanced each other completely. A normal electrocardiogram is uncommon in dynamic and pure rheumatic aortic stenosis.

*Hemodynamic Findings:* Cardiac catheterization studies reveal that combined aortic and mitral stenosis is responsible for a definite reduction in mitral and aortic blood flow and cardiac output.

They also produce an elevation of the mean left atrial pressure, which is less than that seen in patients with pure mitral stenosis. It is a reflection of impaired left ventricular filling, a high end diastolic pressure in the left ventricle, and the elastic qualities of the left atrium during atrial filling. In patients with normal sinus rhythm, the *a* wave predominated while in patients with atrial fibrillation, the *v* wave was of greater amplitude.

The pressure gradients across the mitral valve during ventricular filling are comparable to those in pure mitral stenosis[11] and the calculated mean mitral valve areas are similar. They are significantly below the normal valve area of 4 to 6 cm.$^2$

Another obvious difference between this group and those with pure mitral stenosis is the more marked elevation of pulmonary artery pressure and vascular resistance in the latter. A larger group of cases will have to be investigated to uncover the possible influences responsible for these differences.

A systolic ejection gradient across the aortic valve is seen in every case and the data are quite comparable to those of isolated aortic valve disease.[12] Measurement of flow was not performed in every case, but previous reports have documented the fact that the gradient varies with the rate of flow. It is also related to valve area.

The cross-sectional area of the aortic valve was critically reduced in every case and fell below the estimated normal of 3 cm.$^2$ Only one patient had an aortic valve area greater than 1 cm.$^2$

## RESULTS OF SURGERY

In 1955, it was first reported that surgery was capable of instituting clear-cut objective and subjective improvement in patients with combined mitral and aortic stenosis which was otherwise impossible even under ideal medical regimens. The mortality rate in this previous group of thirty-nine patients was 20.5 per cent.[13]

*Operative Mortality and Causes:* Our present report continues to document the favorable response to combined commissurotomy. The over-all mortality rate in the entire series of 141 cases was less than 20 per cent. The risk of surgery was influenced by the specific technic employed and was nearly twice as high in patients in whom the left atrial and transventricular approach to the two valves was used. The unusually high mortality rate with open mitral and aortic commissurotomy is partially explainable by the fact that the technic was employed chiefly in bad risk patients.

The mortality rate was also related to the presence of leak at either valve. Assessment of the degree of regurgitation in rheumatic heart disease is far from precise although clinical criteria failed to support its presence in a hemodynamically significant form in any of our cases. Direct opacification of the left ventricular chamber was of value in determining how much mitral valve leak was present while aortic insufficiency was appraised in some by the technic of suprasternal transaortic aortography.

The chief cause of death was ventricular fibrillation while the most important hospital complication was the development of congestive heart failure. They were both decidedly more common when the transventricular approach to the aortic valve was employed.

There were nine late deaths and most of these were due to congestive failure. In a review of these cases it was apparent that the unfavorable long term result might be related to the presence of advanced cardiac hypertrophy.

The importance of the myocardial factor in the surgical treatment of aortic stenosis was recently considered in a review of twenty-six patients with massive left ventricular hypertrophy undergoing aortic commissurotomy.[14] The total mortality rate (early and late deaths) in this group was 73 per cent as compared with 39 per cent in the control group with smaller hearts. The various limiting factors in combined aortic and mitral stenosis with advanced cardiac hypertrophy are responsible for this.

*Surgical Complications:* There were six embolic episodes at the time of or immediately after combined commissurotomy. Two of these patients died. Both were operated on by the transventricular approach and the emboli were thought to be particles of calcium separated from the valve substance at the time of the closed aortic commissurotomy.

This incidence of nearly 5 per cent points out the potential dangers of this type of surgery in correcting combined aortic and mitral stenosis. Likewise, the knowledge that nearly one of every ten discharged from the hospital suffered an embolism was disturbing and possibly may point to the need for better technics to correct this type of rheumatic heart disease.

*Clinical Results of Surgery:* Symptomatic improvement was recorded in over eight of ten cases in the follow-up group. Almost completely eliminated were the complaints of nocturnal dyspnea, angina, syncope and vertigo and hemoptysis. This type of clinical improvement has been documented following closed aortic commissurotomy alone.[1]

While objective improvement on auscultation, x-ray examination or electrocardiogram was noted in only four of ten patients, repeat left heart catheterization in some did reveal a fall in the systolic ejection gradient across the aortic valve as well as in the ventricular filling gradient across the mitral valve.

In only one patient was the pressure gradient completely eliminated at the aortic valve and returned to almost normal limits at the mitral valve. This implies that satisfactory mobilization of the valve leaflets may be difficult to obtain and that the postcommissurotomy mitral and aortic valve still may impede normal flow across the orifice.

Since the pressure gradient varies as the square root of the flow, it is apparent that the most ideal type of physiological evaluation entails the measurement of the cross-sectional area of both valves after combined commissurotomy. This study was not carried out in any of our cases although this type of measurement has been recorded following both closed aortic commissurotomy and mitral commissurotomy performed by the left atrial approach.[15] These investigations revealed that closed aortic commissurotomy is capable of increasing the aortic valve area beyond the critical value of 0.6 cm.$^2$ Likewise, in sixteen cases studied before and after left-sided mitral commissurotomy,[16] there was a postoperative cross-sectional mitral valve area greater than 1.5 cm.$^2$ in eleven.

The total experiences following combined commissurotomy therefore appear to be consistent with the results after other types of surgery for stenotic valve lesions and permit us to make the deduction that this type of intervention is capable of modifying the clinical course of this disease. It does not indicate that the operation has been perfected technically or that it will always represent a satisfactory substitute in those areas where open cardiac surgery cannot be performed.

## INDICATIONS AND CONTRAINDICATIONS FOR SURGERY

For the present, it seems best to consider that combined aortic and mitral commissurotomy represents the best therapeutic attack on this form of rheumatic heart disease. Unmistakable evidence has previously been reported of an increase in the severity of coexisting, uncorrected aortic valve lesions when a mitral commissurotomy alone was performed.[17]

There are certain contraindications to this type of surgical intervention. They include the presence of associated mitral or aortic regurgitation, intractable heart failure, rheumatic fever, peripheral cyanosis and arterial oxygen unsaturation (less than 85 per cent). Relative contraindications would include the presence of advanced aortic valve calcification and cardiac hypertrophy.

The surgery should be performed in the presence of those clinical manifestations indicative of pathophysiological changes. At the mitral valve these include dyspnea and fatigue, hemoptysis and emboli. At the aortic valve they include dyspnea and fatigue, angina, vertigo and syncope and nocturnal dyspnea.

If physiological studies are available, the mitral valve area should be less than 1.5 cm.$^2$ and the aortic valve less than 1.0 cm.$^2$ on combined heart catheterization. If left heart catheterization alone is performed, surgery is in-

dicated if the gradient across the mitral valve is greater than 5 mm. Hg during ventricular filling and greater than 20 mm. Hg across the aortic valve during systolic ejection.

Undoubtedly, in the future, this type of surgery will best be performed by open technics utilizing circulatory bypass. Only nine patients were treated in this fashion in this study. Despite the high mortality, it would appear that this method has advantages over closed procedures. A direct attack on either the mitral or aortic valve in a dry field permits exact definition of the commissures and a more accurate commissurotomy. It would seem that the surgeon would have a better chance of establishing valvular mobility and more normal valve action.

## Summary

The clinical features and hemodynamic findings in 141 patients with combined mitral and aortic stenosis are presented. Dyspnea, fatigue, edema and hemoptysis were the most commonly occurring symptoms with angina pectoris, vertigo and syncope being noted less often. The mitral first sound was frequently less sharp than in isolated mitral stenosis and its characteristics were sometimes obscured by the aortic systolic murmur transmitted from the base.

Hemodynamic alterations included a low cardiac index, elevated left atrial, pulmonary arterial and left ventricular systolic pressures and left atrial, left ventricular diastolic and left ventricular-aortic systolic gradients.

Operative mortality by a variety of approaches was 19.2 per cent and improvement in symptoms was noted in 86.6 per cent of the survivors.

## Addendum

Since the submission of this manuscript for publication, eight additional patients have been operated on using the open technic; there was only one death.

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# Symposium on Phonocardiography

## Systolic Triple Rhythms*

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A STUDY of the extra sounds occurring in systole has led us to the conclusion that careful attention to these sounds is of much greater clinical value than is ordinarily believed. There is disagreement as to the proper terminology that should be used when an additional sound is heard in systole. The term *gallop* has been challenged for several reasons. First, the systolic sound is usually high-pitched, clicking and sharp in quality in contrast to the low-pitched, dull quality of the diastolic gallop.[1] Second, the heart rate is usually not rapid so the illusion to a horse's gallop often is not present.[2] Third, the term gallop often implies serious myocardial disease, and this is not necessarily true with systolic sounds.[1–5] The term *systolic click* is also frequently used and is useful but is not adequately descriptive to cover all sounds in systole. For this reason, the term systolic click should not be used. *Systolic triple rhythm* is a better term and does not imply a specific pathogenesis or prognosis.

The purpose of this report is to present, discuss and classify the various sounds that may occur in systole with the exclusion of murmurs.

### PREVIOUS STUDIES

Kuessner (1875), cited by Calo,[5] was the first to advance the possibility that pleuropericardial adhesions were responsible for an additional sound heard in systole. Cuffer and Barbillion[6] described a mid-systolic gallop in six patients, four of whom had typhoid fever, and two tuberculosis. They concluded that the extra sound was due to a double ventricular contraction, a single effort being unable to raise intraventricular pressure sufficiently to cause opening of semilunar valves. Potain[7] popularized the term systolic gallop rhythm. He believed the sound originated from an atheromatous aorta, and others[8–11] agreed with this observation. Obrastzow[9] proposed that the sound was caused by late opening of the semilunar valve due to a prolonged isometric contraction. Gallavardin[12] described in detail the additional systolic sound, which he attributed to tensing of pleuropericardial adhesions. Such adhesions were demonstrated at autopsy in three patients who had no evidence of heart disease. Later, others[13] confirmed the observation of the presence of pleuropericardial adhesions in patients who during life had a systolic triple rhythm.

Orias and Braun-Menendez,[14] in their monograph, devote only a small paragraph to the systolic gallop. Wolferth and Margolies[15] described eight patients with systolic triple rhythms, seven of whom had heart disease. Four of these patients had aortic insufficiency, and three, hypertensive cardiovascular disease. These authors separated the mid-systolic click, presumed to be extracardiac in origin, from systolic gallop, of which they described two types, the *aortic* and *apical*, depending upon the region in which the sound was best heard. These investigators believed that the gallops were definitely due to hemodynamic events occurring in the heart or great vessels. Johnston[16] stressed the inconstancy of the additional systolic sound and concluded that it was an extracardiac phenomenon.

Thompson and Levine,[2] and Luisada and Alimurung,[17] alluded to the fact that systolic triple rhythm is not rare. It occurred in thirty-five of 221 instances (16 per cent) of all

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TABLE I

Clinical Diagnoses in Sixty-Four Cases of Systolic Triple Rhythm

| Diagnosis | No. |
|---|---|
| Congenital heart disease (21 cases): | |
| Interatrial septal defect (ostium secundum) | 4 |
| A-V canal | 1 |
| Eisenmenger's complex | 4 |
| Tetralogy with pulmonary atresia | 2 |
| Idiopathic dilatation of the pulmonary artery | 2 |
| Truncus arteriosus | 1 |
| Mitral atresia | 1 |
| Coarctation of the aorta | 1 |
| Subaortic stenosis | 1 |
| Bicuspid aortic stenosis | 2 |
| Pulmonic stenosis | 2 |
| Acquired heart disease (8 cases): | |
| Mitral stenosis | 2 |
| Mitral insufficiency | 1 |
| Aortic stenosis and insufficiency | 1 |
| Aortic insufficiency (Hufnagel valve in aorta) | 1 |
| Subacute bacterial endocarditis | 1 |
| Right atrial myxoma | 1 |
| Acute myocardial infarction | 1 |
| Disease of the lung, pleura, pericardium or chest wall (9 cases): | |
| Traumatic pleuropericarditis (one case of ice pick injury to aorta and left atrium) | 3 |
| Constrictive pericarditis | 2 |
| Funnel chest | 1 |
| Sarcoidosis | 2 |
| Tuberculosis | 1 |
| Miscellaneous (9 cases): | |
| Periarteritis nodosa | 1 |
| Arrhythmia with auricular sound occurring in systolic cycle | |
| Auricular flutter | 3 |
| Complete A-V block with atrial sound in systole | 2 |
| Nodal tachycardia or nodal rhythm | 2 |
| Thyrotoxicosis | 1 |
| No apparent disease | 17 |
| Total | 64 |

TABLE II

List of Twenty Additional Conditions Accumulated from the Literature in Which a Systolic Sound May be Heard

| |
|---|
| Congenital heart disease: |
| Patent ductus arteriosus[21] |
| Ventricular septal defect[21] |
| Transposition of the great vessels[21] |
| Taussig-Bing syndrome[23] |
| Single ventricle with tricuspid atresia[23] |
| Aortic septal defect[23] |
| Acquired heart disease: |
| Ventricular aneurysm[1] |
| Aortic aneurysm[24] |
| Hypertension[1,15,20] |
| Aortic atheroma[1,15] |
| Nodal tachycardia with retrograde atrial sound[1] |
| Idiopathic pulmonary hypertension[20] |
| Fibroelastosis[23] |
| Disease of the lung, pleura, pericardium or chest wall: |
| Left pneumothorax[1,27] |
| Fibrothorax[1] |
| Mediastinal emphysema[1] |
| Marfan's syndrome[1] |
| Miscellaneous: |
| Typhoid fever[6] |
| Pregnancy[1] |
| Ascites[1] |

gallops in the former series and in twenty-four of 114 (21 per cent) in the latter. Only one-third of the systolic sounds recorded phonocardiographically were audible by the stethoscope in the series reported by Luisada and Alimurung.[17]

The association of systolic ejection clicks with aortic and pulmonic valve lesions, especially stenosis of these valves, and with disease of the aorta and pulmonary artery has recently been stressed.[18–22]

More recently, Minhas and Gasul[23] recorded early systolic clicks in 146 of 598 patients, most of them with congenital heart disease, the majority being below the age of sixteen years. Only eleven showed mid- or late systolic clicks. These authors favor a valvular origin for the aortic and pulmonary ejection clicks since the murmur followed the click in all instances. The presence of an early systolic click was considered to be definitely a pathologic finding.

## Clinical Study

A review of the extra sounds recorded in systole at the Cardiac Department of The Mount Sinai Hospital was undertaken. Sixty-four cases were studied. A Sanborn Stetho-Cardiette, a Tribeam Cardiette, or a Twin-Beam Cardiette was used in all cases. Table I lists the various clinical diagnoses in our series. Twenty additional conditions in which systolic extra sounds have been reported by others are listed in Table II.

From Tables I and II, it can be seen that there are some forty-seven different conditions in which systolic sounds have been recorded. Some form of congenital or acquired (usually valvular) heart disease accounts for approximately 66 per cent of the different etiologies.

## Differential Diagnosis

Systolic sounds must be differentiated from splitting of the first and second heart sounds,

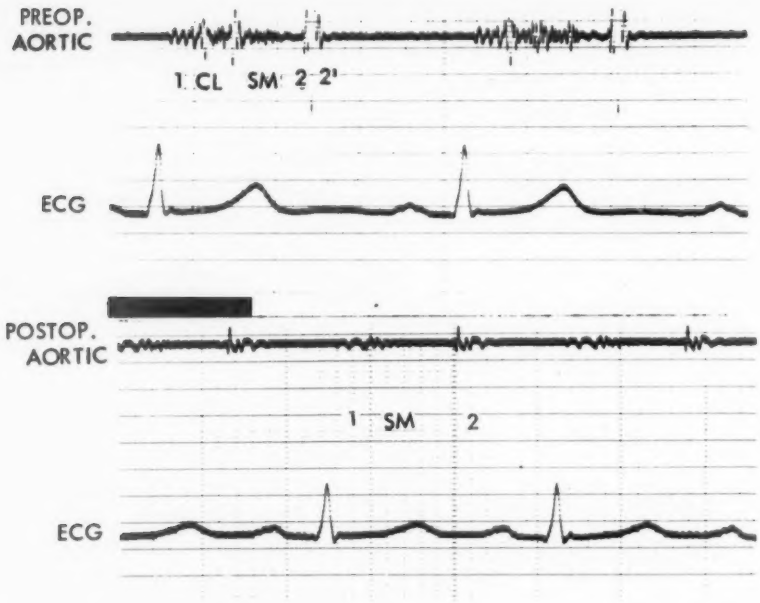


FIG. 1. Preoperative and postoperative phonocardiogram in a proved case of congenital bicuspid aortic stenosis. In the aortic area an early ejection sound (CL) occurring 0.14 second after the onset of the QRS precedes the ejection murmur. The second sound is split. Postoperatively, the ejection sound is no longer present, and the systolic murmur is barely audible.

and from diastolic sounds (such as the atrial fourth sound, the physiologic third sound, the opening snaps of the atrioventricular valves and the diastolic gallops). Timing may be difficult, especially when there is a tachycardia and the diastolic interval shortens. Not infrequently, even the trained observer may err when relying solely upon auscultation, and a phonocardiogram must be obtained to show the precise timing. This was true in several instances in our series.

Abnormal *splitting of the first heart sound* may occur with right bundle branch block due to asynchronism of closure of the atrioventricular valves. Under such circumstances, the splitting may be as wide as 0.05 second.[1] *The second heart sound is normally split* due to asynchronism of closure of the semilunar valves. Deep inspiration may accentuate the physiologic splitting of this sound from 0.03 to 0.08 second.[1,19,22,22a] Wide splitting of the second heart sound up to 0.14 second[22] may occur in severe pulmonic stenosis and may simulate a triple rhythm. *Paradoxical splitting of the second sound*, in which the aortic component of the second sound (normally occurring before the pulmonic) is delayed and follows the pulmonic component, may occur with left bundle branch block, patent ductus arteriosus, aortic stenosis and rarely, systemic hypertension.[25,26] In the pulmonary area, the louder, sharper pulmonary sound preceding the aortic second sound may be mistaken for a late systolic sound.

### Characteristics of Systolic Sounds

An extra sound may occur in early, mid or late systole. It may be sharp, high-pitched and clicking, or low-pitched and muffled. The frequency range of these sounds according to Calo[5] varies from 25 to 100 cycles per second (c.p.s.) and according to Luisada and Alimurung[17] from 10 to 150 c.p.s. The duration of the sound may vary from 0.01 to 0.08 second.[5,17] Not infrequently, the sound may be followed by a murmur, which may be either cardiac or extracardiac in origin.

Certain sounds appear related to specific hemodynamic events and may be constant in timing in relation to the first or second heart sound and independent of the phase of respiration and position of the body. On the other hand, the sound may be extracardiac and wholly dependent upon body position or respiratory phase. The sound may be best heard at the apex, mid-precordium, or base depending upon its origin. Occasionally, the sound may

be reduplicated or multiple. Our observations have shown that these sounds have certain features depending upon their timing in systole, and valuable information can be obtained by knowing their characteristics.

EARLY SYSTOLIC SOUNDS

These are usually *clicks* and show high frequency and high amplitude when recorded by the phonocardiogram (Figs. 1 to 4). Because such sounds are in close proximity to the first heart sound, they may be mistaken for a split first sound or be so closely followed by a murmur as to be unappreciated by auscultation.

Early clicks usually originate from the region of the pulmonary artery and aorta or their respective semilunar valves, and hence are usually best heard at the base of the heart. The aortic ejection clicks are often transmitted to the apex making their differentiation from a split first heart sound difficult.[22a] The early systolic clicks of these cases have been termed the *pulmonary or aortic ejection sound* by Leatham and his associates.[21–23] The pulmonary ejection sound was shown to occur on the average of 0.03 second after the rise of the pulmonary artery pressure curve and hence after the opening of the semilunar valve, which led the authors to conclude that this sound was due to sudden distention of the pulmonary artery. Leatham and Vogelpoel[21] recorded ejection

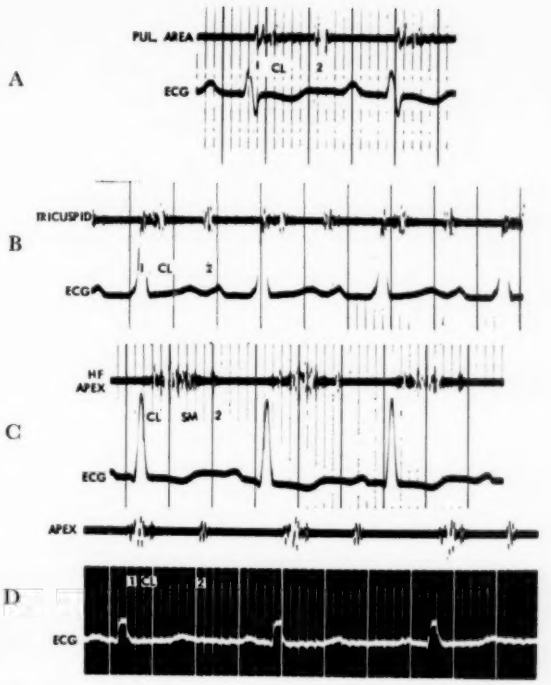


FIG. 2. A, early systolic sound (CL) probably due to rapid ejection in a patient with an atrial septal defect. A systolic murmur follows the ejection sound and the second sound is widely split. B, ejection sound (CL) in a patient with tetralogy of Fallot. C, ejection sound (CL) and typical ejection murmur (SM) in a patient with subaortic stenosis. D, early systolic sound in a patient with coarctation of the aorta.

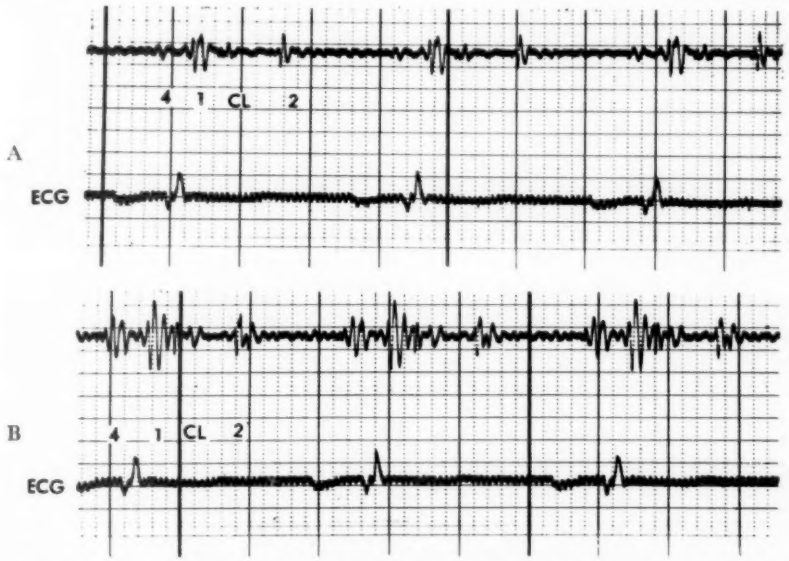


FIG. 3. This illustrates the variability of the intensity of sounds (tricuspid area) with a change in position from sitting (A) to lying (B). The patient had a right atrial myxoma successfully removed with the aid of extracorporeal circulation. In the lying position (supine) the atrial sound (4) and systolic sound (CL) are more clearly evident.

FIG. 4. Early systolic sound (CL). A, in a patient with no heart disease. B, in a patient with Eisenmenger's complex. C, in a patient with a traumatic pleuropericarditis.

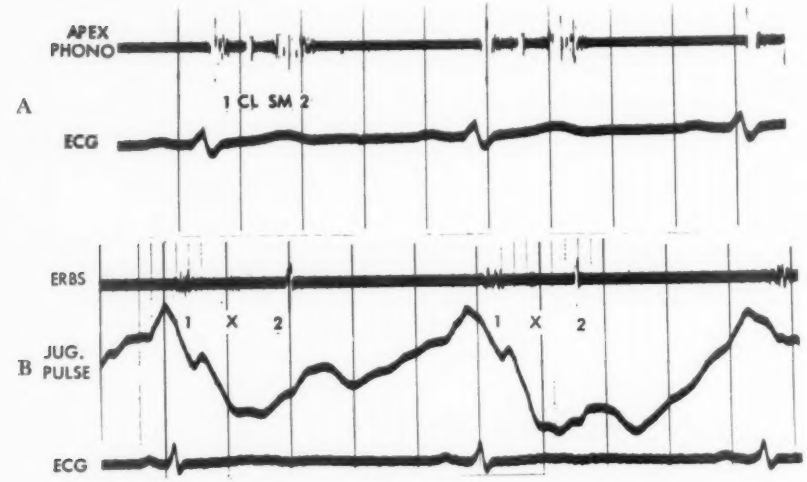


FIG. 5. A, mid-systolic sound (CL) followed by a late systolic murmur in a patient with no heart disease. B, low-pitched mid-systolic sound (*x*) in another patient with no heart disease.

sounds in the following conditions: left-to-right shunts, such as atrial septal defects, ventricular septal defects, and patent ductus arteriosus; mild and moderate pulmonary stenosis; transposition of the great vessels; pulmonary atresia; coarctation of the aorta; aneurysms of the aorta; hypertension; aortic stenosis and aortic insufficiency.

Hultgren[18] has presented evidence that the pulmonary ejection sound is due to a snapping of the inextensible annulus fibrosus. He recorded a click over the annulus that was not present

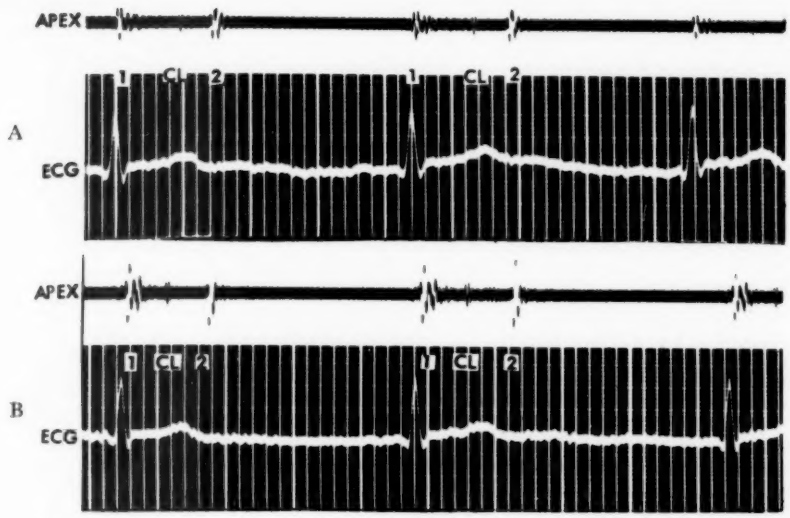


FIG. 6. In this case the systolic sound (CL) which was mid to late in systole (A) occurs earlier on standing (B). Thus, body position may alter the timing as well as be the determining factor of the presence or absence of a systolic sound.

over the great vessels. If a non-elastic, non-constricting band was placed around the aorta or pulmonary artery, the sound could be experimentally produced.

Figures 1 to 4 show early systolic sounds in various conditions. These are usually related to precise hemodynamic events because their timing in relation to the first heart sound is more or less constant. The pulmonary ejection sound is diminished in full inspiration but usually does not disappear.[21] When pulmonary hypertension or aortic insufficiency is present, the ejection sound may be delayed, and, in the latter condition, may be mid-systolic and lower pitched.

In constrictive pericarditis, there may be an early systolic sound in addition to an early diastolic sound.[1] An early systolic sound may be heard in a ventricular aneurysm[1,2,8] and is probably due to the impact of the expanding aneurysmal sac against the chest wall, diaphragm or pleura. When the cause of an early systolic sound is extracardiac, it may be intermittent or vary with respiration or body position (Fig. 8). In patent ductus arteriosus, eddy sounds in systole have been described by Neill and Mounsey.[29]

### MID-SYSTOLIC SOUNDS

Sounds occurring in mid-systole are most often extracardiac in origin (Figs. 5 to 7). They may be clicking in quality or low-pitched, like a diastolic gallop.[4,15] Mid-systolic sounds have been recorded in cases of mitral stenosis, aortic insufficiency, Eisenmenger's complex and ventricular aneurysm. They may occur in malformations of the chest wall, such as pectus excavatum, constrictive pericarditis, pleuropericardial adhesions and fibrothorax. Multiple systolic sounds have been recorded in instances of Mar-

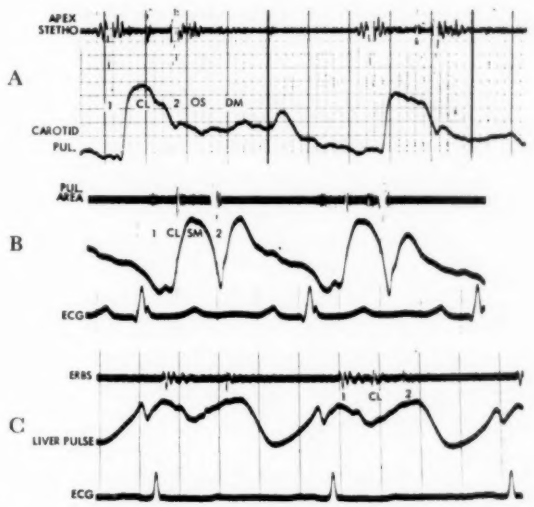


FIG. 7. A, mid-systolic sound (CL) in a patient with mitral stenosis. A loud first heart sound, split second sound, opening snap (OS) and diastolic murmur (DM) are additionally present. B, mid-systolic sound (CL) followed by a systolic murmur (SM) in a patient with Eisenmenger's complex. The pulse tracing (middle tracing) is a combined arterial and venous curve from the carotid area. C, inconstant mid-systolic sound (CL) in a patient with constrictive pericarditis.

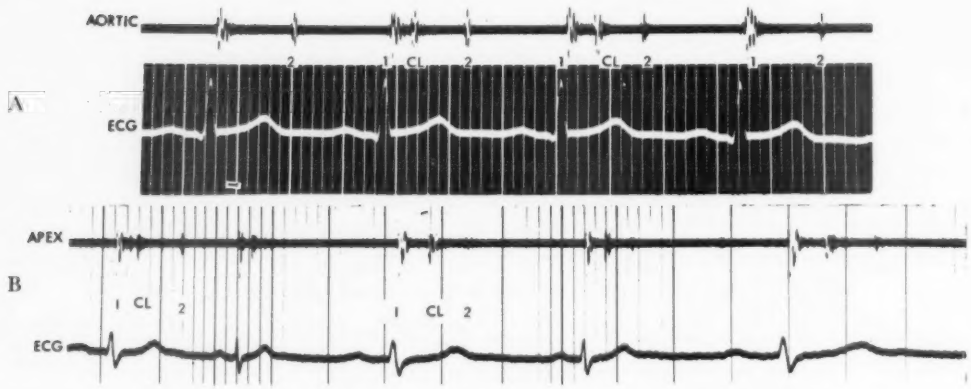


FIG. 8. A, the dependency on a particular phase of respiration for the presence of a systolic sound is clearly demonstrated in this record of a patient with no heart disease. The systolic sound (CL) is present in the second and third cycles, and is earlier in systole in the second cycle than the third. B, systolic sound (CL) varying between early and mid systole.

fan's syndrome and in patients with ascites.[1] The so-called xiphosternal crunch is mid-systolic in timing and best heard at the left sternal border.[30] The "systolic whoop" [31] is mid-systolic and inconstant, but unrelated to respiration or position.

Mid-systolic sounds are usually best heard at the apex or mid-precordium. Not uncommonly, a systolic murmur originates with a click, and extends to the second sound and occasionally into diastole.[5] Often these sounds are dependent upon body position and phase of respiration, which supports the probability that they are extracardiac in origin (Fig. 8).

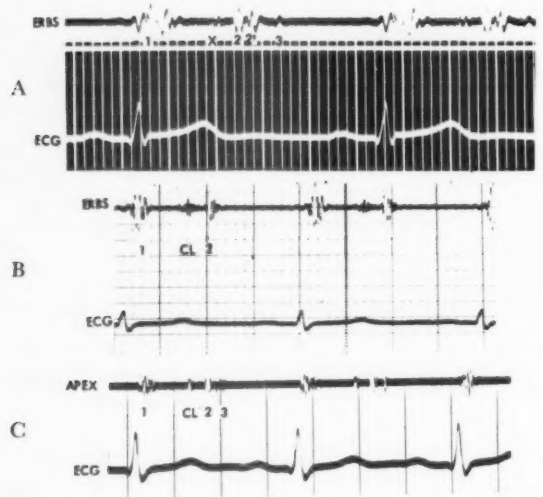


FIG. 9. A, late systolic low-pitched sound (*x*) in a patient with a funnel chest deformity and no heart disease. The second sound is widely split and a third heart sound is present. B, late systolic sound (CL) in a 36-year old male with no heart disease. C, late systolic sound (CL) in a patient with a pleuropericarditis. A third sound is also present.

LATE SYSTOLIC SOUNDS

These are least likely to be caused by hemodynamic events associated with valvular disease or diseases of the great vessels, and are most likely extracardiac in origin (Fig. 9). Pleuropericardial clicks occurring late in systole are usually loudest at the apex or mid-precordium but may be loud or loudest at the base of the heart. Rarely are they heard in the back or abdomen.[5] The quality of the sound may be clicking and sharp, and give the illusion of a split second sound or opening snap. When low-pitched, the sound may simulate a diastolic gallop. In cases of pericarditis, the friction rub may be preceded by a click. Late sounds may disappear, decrease in intensity, or become more mid-systolic or even early systolic with change of body position or respiratory phase. They may, however, be constant in timing and persist for years.[5]

It has been previously stated that the mid- and late systolic sounds may occasionally be associated with a murmur. When present, the click usually precedes the murmur. It occurs when there are no important hemodynamic events occurring, that is, after rapid ejection and when there is no valve movement. The heart is moving in relation to thoracic structures, and thus the origin of both the click and murmur are presumably extracardiac.

ATRIAL SOUNDS

The fourth or atrial sound occurs in presys-

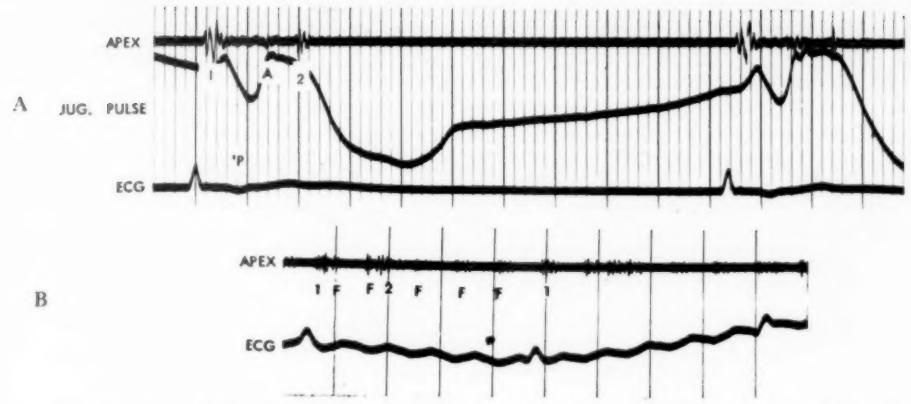


FIG. 10. A, nodal bradycardia with retrograde atrial conduction (inverted P wave following QRS complex). A low-pitched systolic sound (*A*) is present 0.11 second after the onset of the P wave and this probably is an atrial sound. B, atrial flutter with multiple low pitched sounds (*F*) regularly spaced throughout systole and diastole.

tole. In certain instances, atrial sounds may be heard in systole (Fig. 10). In atrial flutter, multiple low-pitched sounds may be heard at regular intervals throughout systole and diastole. In addition, we have recorded such atrial sounds in systole in cases of nodal rhythm and ventricular tachycardia with retrograde atrial conduction, and in instances of complete heart block.

### PROPOSED CLASSIFICATION

It has been frequently pointed out that systolic clicks or gallops are usually benign, in the sense that generally no heart disease is present.[1–3,5,16,17,32,33] However, approximately 70 per cent of the patients in our series had heart disease. In all of these, a murmur was additionally present. Excluding these, the remainder of the patients had no evidence of heart disease. It seems appropriate, therefore, to classify systolic sounds into two basic categories as follows: (1) early systolic sounds accompanied by a murmur (usually a valvular disease or a lesion of the great vessels is present); and (2) late or mid-systolic sounds with or without murmurs (cardiovascular disease is usually absent) (Table III). Exceptions to this classification exist; for example mid-systolic sounds may be associated with cardiovascular disease and, in instances of ventricular aneurysms and constrictive pericarditis, there may be an early, mid- or late systolic sound without a murmur in the presence of significant myocardial disease. With a thorough understanding of the charac-

TABLE III
Characteristic Features of Systolic Extra Sounds

| Origin | Quality | Timing | Area of Maximal Intensity | Relationship to First or Second Heart Sound | Major Examples | Differential Diagnosis | Exceptions |
|---|---|---|---|---|---|---|---|
| Cardiovascular | Click, rarely low pitched; usually associated with a murmur | Usually early, occasionally mid, rarely late in systole | Usually base of heart | Usually constant and not affected by respiration or change of position | Aortic stenosis, pulmonary stenosis, pulmonary hypertension, left-to-right shunts | Split first heart sound, presystolic gallop | Occasionally extracardiac and pericardial clicks may be early and associated with a murmur or bruit |
| Extracardiac (and pericardial | Click or lower pitched sounds; murmur may or may not be present | Usually mid or late and rarely early | Apex or midprecordium | Inconstant relation to first or second sound, often affected by change in position or respiration | Pleuropericardial adhesions, constrictive pericarditis, chest wall deformities | Diastolic gallops, split $P_2$ and opening snap | Ventricular aneurysms |

teristics of systolic sounds, their significance may be correctly interpreted. Table III lists the major features of each category.

## Summary

1. The records of sixty-four cases of systolic triple rhythm have been reviewed. The presence or absence of cardiovascular disease and the various characteristics of these sounds were evaluated.

2. Systolic triple rhythms are probably more frequently present than generally suspected and may be heard in a wide variety of cardiac and extracardiac diseases.

3. Early systolic clicks are ejection sounds and are found in patients with congenital and acquired lesions of the semilunar valves and great vessels and are usually associated with a murmur.

4. Mid- or late systolic sounds may or may not be associated with a murmur and are usually not observed in patients with cardiovascular disease.

5. With a thorough understanding of the characteristics of systolic sounds, their significance may be correctly interpreted.

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# Apical Diastolic and Presystolic Murmurs of Proved Functional Nature*

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THE POSSIBILITY of apical diastolic and presystolic rumbles caused by a "functional" mechanism, i.e., without mitral stenosis, has been known for a long time. Clinical reports first described such murmurs in aortic regurgitation,[1] pericardial or hypertensive heart diseases,[2] rheumatic heart disease without mitral stenosis,[3–7] and myocarditis.[8] Subsequently, phonocardiographic studies documented such murmurs in rheumatic, coronary, hypertensive and congenital heart diseases.[9–13,18,19] A recent study by Hubbard et al.[14] analyzed the mid-diastolic rumble of patients with pure mitral insufficiency.

Three previous reports from our group[15–17] described numerous such cases, proved the functional nature of the murmurs by autopsy or through disappearance of the murmur, and described the graphic characteristics of the "functional" murmur.

In spite of such impressive evidence, the classic teaching that a diastolic or presystolic rumble is *always* organic in nature still prevails. For this reason, it was considered that a new comprehensive study was indicated.

## MATERIAL AND METHOD

The present study consists of three parts:

1. A comparison between phonocardiographic documents and autopsy reports from 1948 to 1958. Since no autopsy record was available for many patients studied by phonocardiography, it is obvious that the number of cases thus studied represents only a small percentage of the total group of functional diastolic rumbles. This group includes nine patients having no mitral lesion at autopsy in whom the clinical and phonocardiographic data revealed an apical diastolic or presystolic rumble.

2. A study of ten patients with congenital heart disease in whom the diagnosis was proved by right heart catheterization and the phonocardiogram revealed an apical diastolic or presystolic rumble.

3. A study of thirteen patients with clinical and phonocardiographic evidence of apical diastolic or presystolic rumbles in whom left heart catheterization failed to prove a gradient across the mitral valve (a mimimal gradient was found in one).

*Clinical study* of the thirty-two patients was made in the cardiac clinics, wards and private floors of Mount Sinai Hospital but the physical findings were checked and recorded by a cardiologist prior to the phonocardiographic study. An electrocardiogram was always recorded; a pulse tracing was recorded in several cases.

The *phonocardiograms*, with the exception of a few older tracings, were recorded as follows: (1) a standard "stethoscopic" tracing by means of a Sanborn twin-beam; (2) a "filtered" tracing in the various octaves according to the description given in 1956[20] but with the modifications recently suggested by one of us with Zalter.[21–23]

*Cardiac catheterization* was performed in this laboratory as follows: (1) In patients with a tentative diagnosis of congenital heart disease: right heart catheterization with recording of pressures and phonocardiograms† from the various chambers plus collection of blood samples for oxygen determination. (2) In patients with a diagnosis of mitral or aortic valve disease: both right and left heart catheterizations. The latter was performed by the transthoracic approach according to the technic of Bjoerk modified by Fisher. Pressures and phonocardiograms were recorded from the various chambers of the left heart. A pullback maneuver from the left ventricle in the left atrium was repeatedly made in all cases. Some patients were given an intravenous infusion of norepinephrine in order to increase the systolic pressure of the left ventricle according to the suggestion of Braunwald et al.[25]

* From the Department of Medicine and the Divison of Cardiology, The Chicago Medical School, Chicago, Illinois. This study was made under the tenure by Dr. Luisada of a teaching grant of the National Heart Institute, U. S. Public Health Service.

† The intracardiac phonocardiogram was recorded by using a method described in this laboratory.[24]

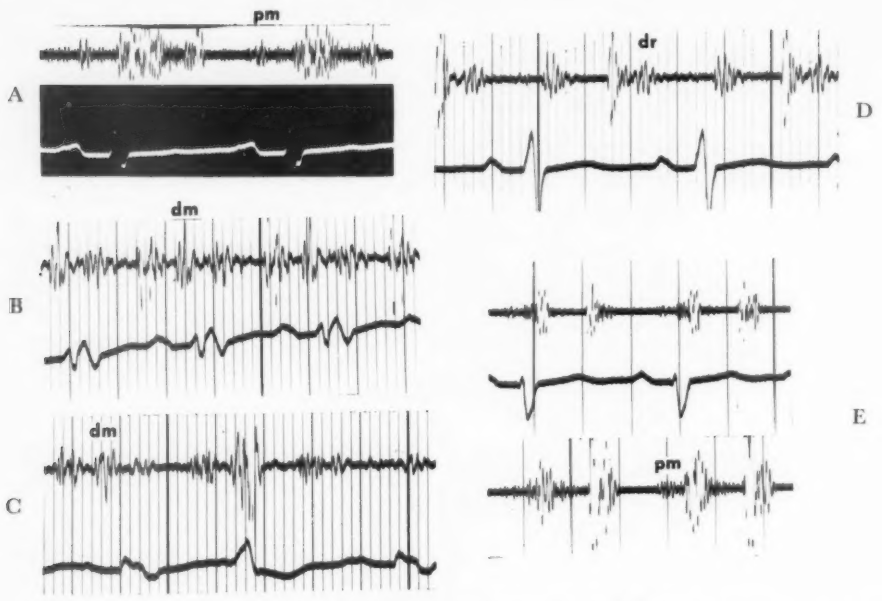


FIG. 1. Diastolic rumbles in cases in which autopsy excluded any valvular stenosis. A, Case 7. Atrial septal defect; cleft of mitral and tricuspid valves. Presystolic rumble (stethoscopic tracing, apex). B, Case 6. Viral myocarditis. Irregular, low-pitched diastolic rumble (stethoscopic tracing, apex). C, Case 4. Myocarditis. Presystolic rumble (stethoscopic tracing, apex). D, Case 3. Coronary heart disease; recent myocardial infarct. Early diastolic rumble (stethoscopic tracing, apex). E, Case 8. Cor pulmonale; multiple pulmonary thrombosis. Presystolic murmur, systolic murmur, split second sound. *Above*, stethoscopic tracing, mid-precordium. *Center*, electrocardiogram. *Below*, filtered tracing (band 60–120), mid-precordium.

## RESULTS

*Autopsy Cases* (*Fig. 1*): The main etiologic factors are presented in Table I. It is likely that in the cases of cor pulmonale and congenital heart disease the murmur originated in the right ventricle, which formed most or all of the anterior surface of the heart. A clinical diagnosis of mitral stenosis was made in three patients (Cases 6, 7 and 8). The phonocardiogram excluded such a diagnosis in two (Cases 6 and 7), while a stenosis was admitted in one (Case 8), partly because an extra sound was recorded in early diastole (tricuspid snap?).

While the vibrations of the murmur were often mid-diastolic and of fairly large amplitude, they were presystolic, somewhat smaller and of a higher pitch in three patients (Cases 1, 7 and 8), and diastolic-presystolic in another (Case 6) (Table II). In Case 1, the finding of a presystolic murmur in the phonocardiogram led to an erroneous graphic diagnosis. It should be mentioned that had the clinical picture been less typical in Cases 3 and 4, an erroneous clinical diagnosis would also have been made in them.

*Patients Studied by Right Heart Catheterization Alone* (*Fig. 2*): All these patients had a clear clinical, electrocardiographic and roentgenological picture of congenital heart disease. One had pulmonic stenosis, two a ventricular septal defect and seven an atrial septal defect. A diastolic or presystolic rumble was recorded clinically in four patients (Cases 10, 12, 13 and 18) and a question of mitral stenosis was raised in one (Case 13).

The recorded murmur was presystolic in five patients, early diastolic or mid-diastolic in two, and diastolic-presystolic in two. It was generally of medium-low frequency. In the atrial septal defects, the murmur was often recorded at the base, sometimes on both sides of the sternum. In some of the patients it was well recorded in the third to fourth left interspaces.

*Patients Studied by Both Left and Right Heart Catheterizations* (*Fig. 3*): A diastolic or presystolic murmur was heard clinically in all but two patients (Cases 21 and 27), while in Case 30 a gallop sound was heard. In all of them, diastolic vibrations were recorded. They were presystolic in five patients, and early diastolic or mid-diastolic in the others. The murmurs were of either medium-low or medium-high

TABLE I

Apical Diastolic or Presystolic Rumbles Proved of Functional Nature

| Etiology | No. of Cases |
|---|---|
| Coronary heart disease | 4 (autopsy in 3, left heart catheterization in 1) |
| Myocarditis | 4 (autopsy in 2, left heart catheterization in 2) |
| Chronic cor pulmonale | 3 (autopsy in 3, also right and left heart catheterization in 1) |
| Congenital heart disease: | |
| Atrial septal defect | 8 (autopsy in 1, right heart catheterization in 7, surgery in 1) |
| Ventricular septal defect | 2 (right heart catheterization in 2) |
| Pulmonic septal defect | 1 (right heart catheterization) |
| Rheumatic heart disease: | |
| Mitral insufficiency | 3 (left and right heart catheterization) |
| Aortic insufficiency (Austin Flint) | 2 (left heart catheterization) |
| Minimal mitral stenosis | 1 (left heart catheterization) |
| Syphilitic heart disease: Aortic insufficiency (Austin Flint) | 1 (left heart catheterization) |
| Unknown | 3 (left and right heart catheterization) |

frequency, and in certain patients were indistinguishable from the typical murmurs of mitral stenosis (Figs. 3C and 3F).

With the exception of one patient (Case 28), no gradient was found across the mitral valve. Some of the patients had a high diastolic pressure in the left ventricle (Cases 21, 23, 26, 27 and 29) and this may have caused a more powerful presystolic contraction of the left atrium. It is noteworthy that only one patient (Case 25) had an opening snap of the mitral valve. In Case 22 the diagnosis of fibroelastosis was advanced but so far no definite proof has been obtained.

In two patients (Cases 23 and 25), the absence of a mitral gradient might still have been consistent with a "dynamically insignificant" mitral stenosis (see Case 28).

TABLE II

Features of Apical Rumbles

| Features | No. of Cases |
|---|---|
| Timing: | |
| Early or mid-diastole | 13 |
| Presystole | 14 |
| Both phases | 5 |
| Frequency: | |
| Predominance of medium or low frequency vibrations | 21 |
| Predominance of high frequency vibrations | 11 |
| Amplitude: | |
| Small amplitude in relationship with heart sounds | 16 |
| Large amplitude in relationship with heart sounds | 16 |

Case 28 deserves special discussion. The patient was a seventeen year old student nurse with no previous history of cardiac disease. In 1957 a routine check-up disclosed a diastolic-presystolic murmur and a faint systolic murmur (Fig. 4A), and a diagnosis of mitral stenosis and insufficiency was made. The electrocardiogram was normal. Six months later, following strenuous exertion, the patient experienced dizziness and had a severe episode of dyspnea lasting for several hours. She was admitted to Mount Sinai Hospital, and given sedatives and digitalis. At that time mitral commissurotomy was discussed. Following discharge, the patient went home but returned a year later.

At this time both auscultation and phonocardiography failed to reveal any presystolic murmur (a minimal diastolic murmur was present in the filtered tracing; Fig. 4B). However, intravenous infusion of Levophed® caused the appearance of a large early diastolic murmur (Fig. 4C). Left heart catheterization revealed a minimal gradient across the mitral valve (less than 3 mm. Hg) and no increase of the latter with Levophed. Nine months later the patient returned for a check-up. At this time only a systolic murmur in decrescendo was found (Fig. 4D).

The final conclusion was that in spite of the absence of clinical or laboratory evidence, the patient had acute rheumatic fever in 1957. This caused the minimal mitral lesion found in 1958. The insufficiency seemed to be increasing in 1959. The actual cause of the large presystolic vibrations was later considered to be functional.

## Comments

The problem of apical or mid-precordial diastolic and presystolic rumbles simulating those of mitral stenosis has considerable clinical importance. In spite of the accumulating evidence revealing how often a diastolic murmur is due to functional factors, the classic teaching that this "cannot happen" is still prevalent.

In the auscultation of a patient, a mid-precordial rumbling diastolic murmur may be noted because of one of the following possibilities:

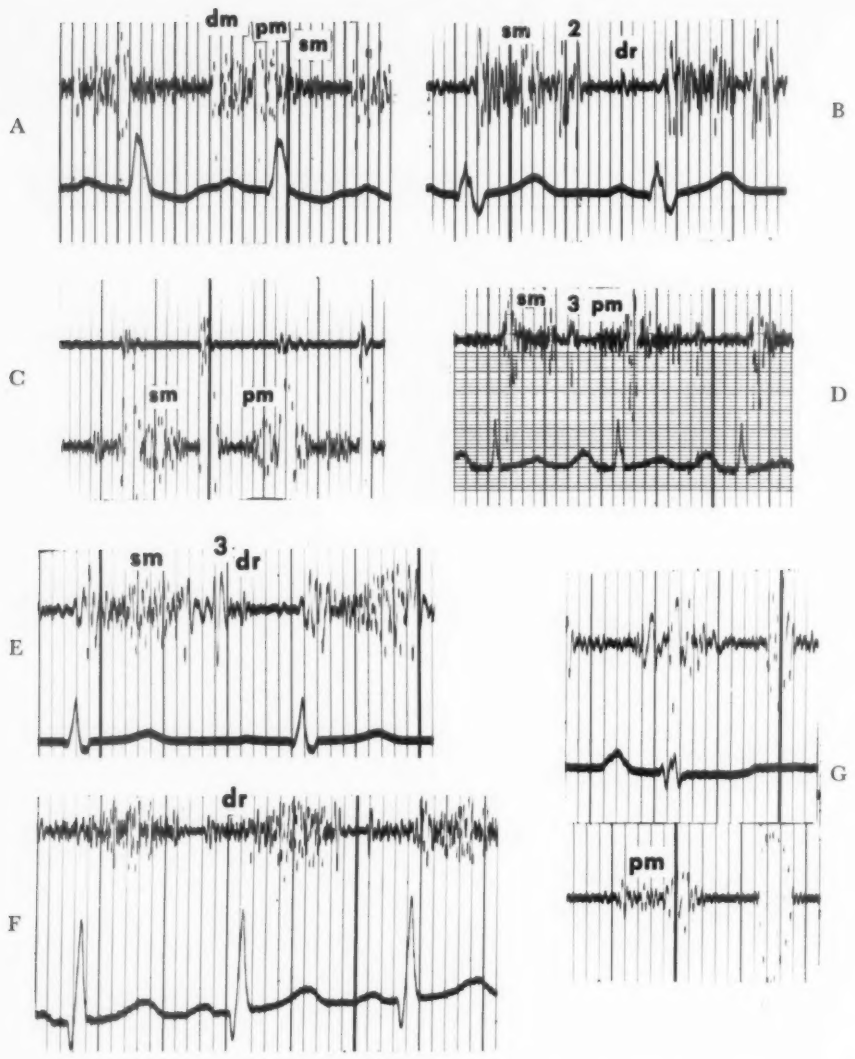


Fig. 2. Diastolic or presystolic murmurs in cases of congenital heart disease. A, Case 18. Ventricular septal defect with bidirectional shunt. Large diastolic-presystolic rumble, systolic murmur (stethoscopic tracing, apex). B, Case 14. Atrial septal defect. Large systolic murmur, split second sound, small diastolic rumble (stethoscopic tracing, mid-precordium). C, Case 17. Atrial septal defect. Systolic murmur, presystolic murmur. *Above*, stethoscopic tracing at low amplitude. *Below*, filtered tracing (band 60–120), tricuspid area. D, Case 12. Atrial septal defect. Systolic murmur, large third sound, presystolic murmur (stethoscopic tracing, tricuspid area). E, Case 15. Ventricular septal defect. Large systolic murmur, large third sound followed by a small diastolic murmur with a snap (stethoscopic tracing, apex). F, Case 13. Small atrial septal defect. Large systolic murmur, diastolic-presystolic murmur initiated by a third sound (stethoscopic tracing, apex). G, Case 10. Atrial septal defect. Presystolic murmur; in the *upper* tracing (stethoscopic, apex) there is a large, low-pitched fourth sound, in the *lower* tracing (filtered, band 60–120), this vibration is not visible.

1. It is an *unwarranted auscultatory illusion*, often dispelled by repeated auscultations. The phonocardiographic tracing shows a clear diastolic line.

2. It is a *warranted auscultatory illusion*. The phonocardiogram shows a crescendo type of first sound.

3. It is due to *misinterpretation of certain aus-*

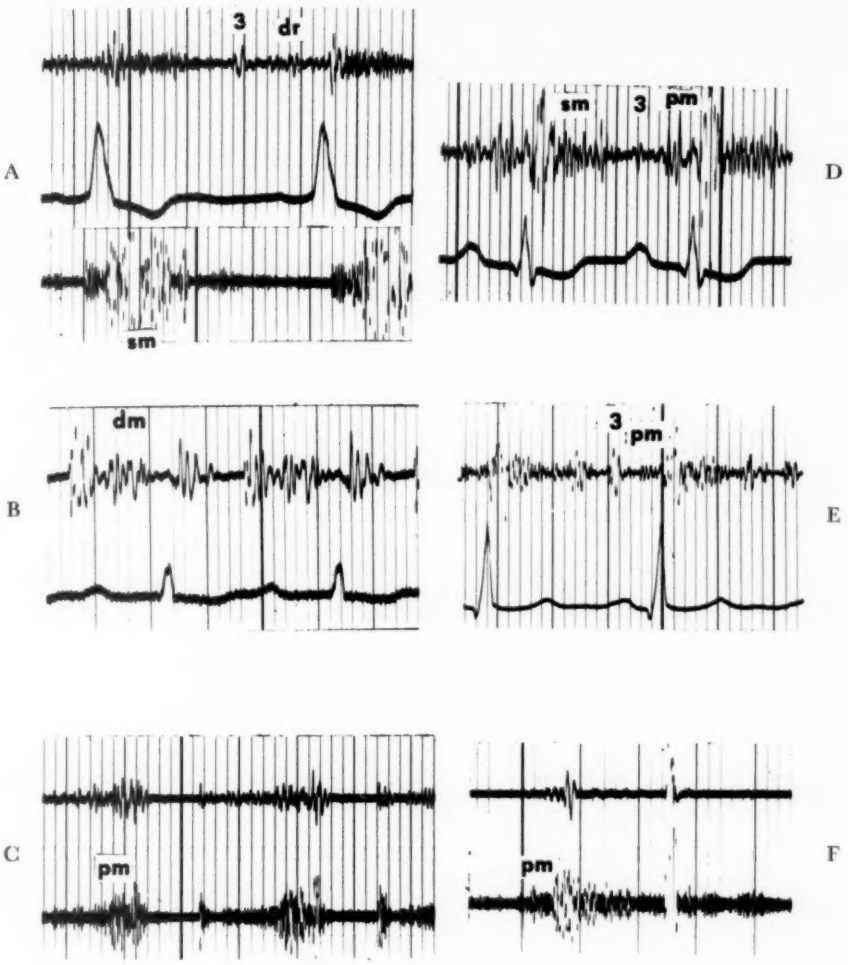


FIG. 3. Diastolic or presystolic murmurs in cases in which left heart catheterization proved there was no gradient or one smaller than 3 mm. across the mitral valve. A, Case 21. Aortic insufficiency and stenosis, no mitral gradient. Large systolic murmur; large, low-pitched third sound; small, low-pitched mid-diastolic rumble (*upper tracing*). The *lower tracing* (filtered, band 150–250) fails to show the murmur. B, Case 19. Primary pulmonary hypertension, no mitral gradient. Mid-diastolic rumble of low pitch (stethoscopic tracing, mid-precordium). C, Case 22. Fibroelastosis? Diastolic-presystolic rumble in crescendo. *Above*, stethoscopic tracing. *Below*, filtered tracing (band 240–1,000), within apex. No mitral gradient; high diastolic pressure of left ventricle. D, Case 23. Severe mitral insufficiency, no mitral gradient. Large systolic murmur in decrescendo; third sound; presystolic murmur (stethoscopic tracing, apex). E, Case 24. Severe mitral insufficiency, no mitral gradient. Systolic murmur in decrescendo: large, prolonged third sound; small presystolic murmur (stethoscopic tracing, apex). F, Case 25. Aortic insufficiency, no mitral gradient. Systolic murmur in decrescendo; early diastolic murmur in decrescendo; presystolic murmur in crescendo. *Above*, stethoscopic tracing, underamplified. *Below*, filtered tracing (band 200–400), apex.

*cultatory phenomena* occurring during diastole (diastolic or presystolic type of triple rhythm; quadruple rhythm), usually in patients with ventricular overload, or during systole (systolic type of triple rhythm). In these patients the phonocardiogram easily reveals the clinical error.

4. It is due to *auscultation of an opening snap* of the mitral valve. Even though it is not correct to interpret this as a "murmur," the

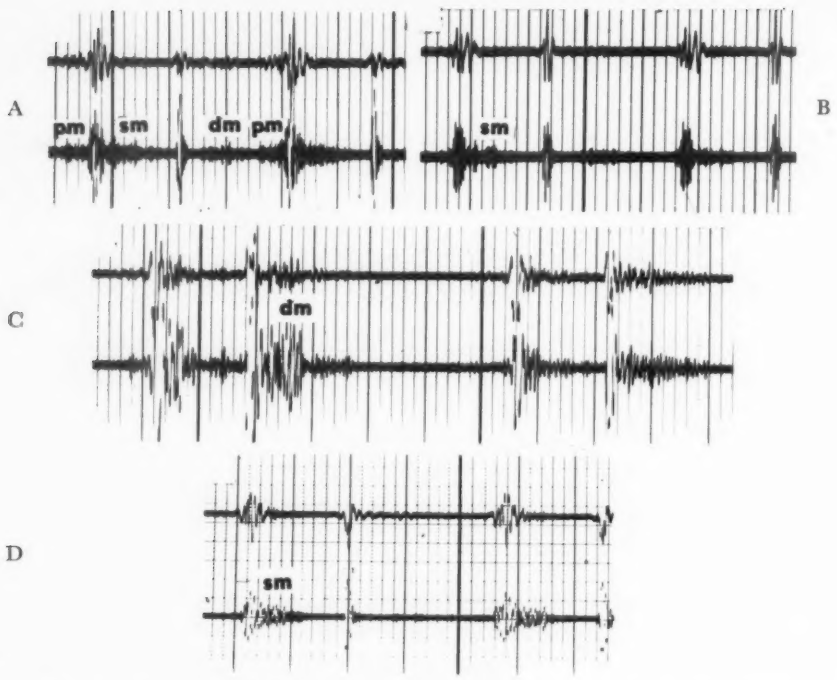


FIG. 4. Case 28. Probable acute rheumatic fever. A, September 1957. Low-pitched presystolic and mid-diastolic murmurs with high-pitched overtones; high-pitched systolic murmur. *Above*, stethoscopic tracing, apex. *Below*, filtered tracing 120–240. B, March 1958, just prior to left heart catheterization. The diastolic and presystolic murmurs have sharply decreased. *Above*, stethoscopic tracing, apex. *Below*, filtered tracing 120–240. C, same day as (B), following infusion with norepinephrine: appearance of large early diastolic murmur. *Above*, stethoscopic tracing, apex. *Below*, filtered tracing 60–120. D, January 1959. Disappearance of diastolic murmurs, larger systolic murmur. *Above*, stethoscopic tracing, apex. *Below*, filtered tracing 120–240.

diagnosis of mitral stenosis is then warranted. The phonocardiogram shows the snap in early diastole.

5. It is due to a *minimal narrowing of the mitral valve* which is not sufficient for the creation of a gradient of pressure. According to Selzer et al.,[26] the mitral area must be reduced to less than one-half the normal surface (or less than 2 sq. cm.) to cause a gradient. Therefore, in these patients (Cases 23 and 25) one might admit the existence of a "dynamically insignificant mitral stenosis."

6. It is due to a *diastolic or presystolic rumble of functional nature*. In most of the cases the phonocardiogram reveals the functional origin of the murmur by the following graphic characteristics of the latter: (a) It starts at mid-diastole with a large third sound or can be considered as a prolongation of the third sound (Figs. 1B, 1D and 3B). If presystolic, it is not in crescendo (Figs. 1B, 1C, 2C and 3D). (b) It has a high amplitude (Figs. 1B, 3B and 3D). (c) It can be recorded over a wide area of the precordium. On the other hand, in a few cases even the phonocardiogram may not reveal the nature of the murmur (Figs. 2A, 2C, 2D, 2F, 3C, 3F and 4A) because this murmur is similar to that of mitral stenosis.

In these cases, attention should be paid to certain negative data (absence of an opening snap, frequent absence of a split $P_2$) plus the possible recording over a wide precordial area. Collateral data (normal electrocardiogram, left axis deviation or left bundle branch block, normal left atrial shadow on x-ray film) may be of importance in the differential diagnosis.

## SUMMARY

We have collected a series of thirty-two clinical cases in which a diastolic or presystolic murmur simulating that of mitral stenosis was recorded in the phonocardiogram. The functional nature of the murmur was proved in nine by autopsy, in ten by right heart catheterization

(pulmonic stenosis or septal defect), and in thirteen by left heart catheterization, which revealed the absence of a mitral gradient.

A clinical error was made in most cases, except those in which an entirely different clinical picture was present (congenital heart disease, recent myocardial infarct).

The phonocardiogram was correctly interpreted in most cases. However, in five cases the tracing was interpreted as being consistent with mitral stenosis. In two of them a "dynamically insignificant" mitral stenosis was suspected, although *not proved*. In the other three, no stenosis whatsoever was finally admitted.

A case in which the murmur was probably due to acute rheumatic carditis is discussed in detail and repeated tracings are presented.

The various causes which can lead to a clinical error are listed and it is shown that, in many of these cases, a phonocardiogram helps to rule out mitral stenosis.

It is further shown that in a few exceptions even the phonocardiogram can be misinterpreted. Left heart catheterization often reveals the absence of a mitral block thus reducing the doubtful cases (dynamically insignificant lesion) to a minority.

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# Seminar on Ballistocardiography*

## A Clinician's Approach to the Ballistocardiogram†

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THE APPROACH of a practicing physician to new instruments and new ideas is different from that of the research specialist or the full-time hospital physician. Unless the new instrument is of immediate practical value for the practice of medicine, the average physician does not have time, space or money to divert to its trial.

My interest in ballistocardiography relates to the first time when I noted that the record was in some way related to cardiac strength.[1,2] It seemed to me that if the physician could gain some true appraisal of the patient's heart strength, he would be better able to care for him and predict the future course of his illness. Current clinical methods offered no suggestion of the strength of the heart until it had completely failed. Neither blood pressure, palpation of the pulse, pulse wave records or the stethoscope could give this type of information.

My first experience with the ballistocardiograph was with Starr's high frequency table. This was, however, still very much a laboratory research instrument, both in size and cost. For the practical purpose of fitting into a busy office or hospital routine, an instrument was needed that would trace the ballistocardiogram through the usual electrocardiographic recording instruments. This need was met by the shin bar apparatus of Dock.[3] This method was far from ideal since problems of standardization of the equipment and calibration of the tracings are great.

Although improved methods of recording ballistocardiograms have been developed,[4–9] in my office practice, currently, I still use the shin bar method. Admittedly, the tracings are quite crude and lacking in detail, but one becomes quickly trained to distinguish a normal from a grossly abnormal tracing and this is the limit for which I use this particular apparatus. In those cases in which a more detailed examination is required, I make use of the Starr bed at the hospital. When the differential diagnosis is not simply between a "good" or a "bad" heart, and a detailed study of the minutiae of wave form is required, particularly for those patients exhibiting problems of ventricular asynchronism, I use the ultra low frequency apparatus available in Dr. Starr's laboratory. There is little question that the most detailed ballistocardiograms are secured from this apparatus, but it is both delicate and space-consuming, requires time and patience to secure a good tracing and must be handled with care.

### EXPLANATION OF BALLISTOCARDIOGRAPHIC THEORY

One of the duties of the clinician is to explain to his students what he has in mind when he orders a ballistocardiographic study. Such an explanation must be given with the assumption that the listener has little, if any, knowledge of mathematics and that such terms as force, frequency, damping and rate of change either

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have no exact meaning or are altogether meaningless. The simple analogy to firing a gun, feeling the recoil kick and noting the impact of the bullet striking the target is first used.

Most people see the point clearly if one draws an analogy to a gun and target, both mounted on a table free to move (Fig. 1). The gun fires; first, the recoil drives the table to the right, and then an instant later the impact of the bullet on the target pushes it to the left. Everyone can see at once that the larger the charge of powder, the greater these movements would be and that, even if one could observe nothing but the table's movements, an estimate of the size of the charge of powder would be easy. Also thinking of two guns attached to the same table, it may be seen that if they did not fire together the movement of the table would be distorted. From this example a second idea is readily grasped by most people: that if the forces from the two sides of the heart were not delivered together, the contour of the record would be affected.

A better analogy is secured if one substitutes for the gun a hose discharging a stream of water at the target. When the hose is turned on, during the interval before the stream strikes the target, the jet effect pushes the table to the right. When the stream strikes the target its impact balances the jet effect. When the stream is turned off at the hose nozzle, there is an interval when the jet effect has ceased but the impact on the target continues, and the table moves to the left.

Most people see this easily and are now in a position to visualize the more complicated situation of the heart rhythmically discharging its blood into curved tubes, the aorta and pulmonary artery. They now see that when the heart ejects its blood in a headward direction the recoil from this ejection drives the body footward initially. An instant later, when the moving blood reaches the arch of the aorta and the curve of the pulmonary artery, the headward movement of most of it is arrested, giving an impact which drives the body headward.

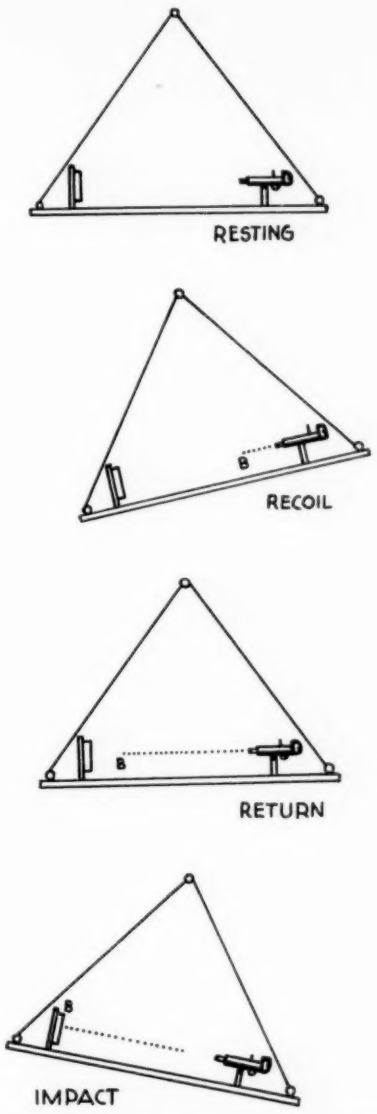


FIG. 1. Simplified explanation of ballistic force producing the ballistocardiogram by analogy to the firing and recoil of a gun and the impact of a bullet striking a target (see text).

Doctors need to be reminded that ballistic asynchronism of the two sides of the heart, a cause of notching of the waves, can be due altogether to a difference in the contour of the right and left heart ejection curves, and does not imply that the contraction of one side of the heart either begins or ends at a time different than the other.

A diagram of hypothetic pressure curves in the aorta and pulmonary artery may be of aid in visualizing this point, for doctors are accustomed to looking at pressure curves while curves of flow are unfamiliar (Fig. 2). In

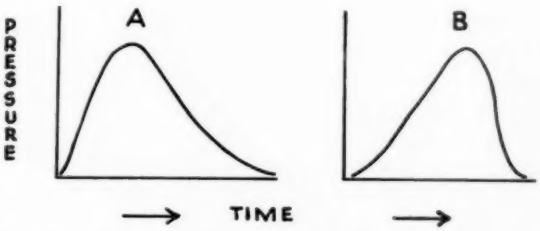


FIG. 2. Diagram of hypothetic pressures in the aorta. A, rapid early rise in pressure, from strong force early in the systole. B, pressure rising slowly to late peak, from weaker force acting more slowly.

example (A) the pressure rises rapidly to a peak. This curve may be expected to result from a strong force delivered early in systole; let us think of it as a contraction starting with a good jerk. In example (B) the pressure rises slowly to a late peak. This curve may be expected to result from a weaker force acting more slowly from a feeble contraction, but the duration of the rise in pressure above the base line, determined by the duration of systole, may be identical in the two instances.

Ballistocardiographic asynchronism may result from a different time of onset or cessation of ejection from the two sides of the heart. It can be accepted also that ballistic asynchronism can arise from differences in the forces delivered during systole when one ventricle contracts more weakly than the other through the same time interval.[6]

## Detection of Heart Disease

In a considerable proportion of the patients who come to me with suspected heart disease, or a fear of having it, the routine clinical study leaves me still in doubt. In these I use the ballistocardiogram to help resolve this doubt. There is the group of patients who already have been informed that they have heart disease, often from electrocardiographic evidence such as bundle branch block or unstable T waves of a questionable kind. If I find a normal ballistocardiogram in such cases, I am able to reassure the patients with increased confidence.

Many doctors have had the experience of examining a patient who is worried about himself and suffering with indefinite symptoms. After finding that the routine cardiac examination showed no abnormalities and reassuring the patient, either sudden death or a serious cardiac episode soon followed. I have no expectation that the ballistocardiogram will provide a complete answer to problems of this kind. Certainly some types of cardiac damage, such as that from an embolus originating in a place remote from the heart, would not necessarily be associated with a prior deterioration of cardiac function. However, damage from coronary sclerotic lesions might well throw a shadow before it by affecting cardiac performance before the acute event. In many autopsies the coronary arteries are found to be sclerotic even though the patient, dying from another cause, never had a symptom suggesting heart disease. It is therefore doubtful that better history taking is the whole solution. Knowledge of the abnormalities of cardiac performance so often demonstrated by the ballistocardiogram in older persons without clinical evidence of heart disease, however, might well be a help in improving our ability to detect a cardiac disorder before acute symptoms appear and so reduce the number of these embarrassing failures.

### Ventricular Asynchronism

Several years ago the director of the medical department of a large railroad, who occasionally had sent patients to Dr. Starr for a ballistocardiogram, consulted him about one of their engineers who had suffered an attack of pulmonary edema while at the throttle of his train and only with difficulty had brought it to a stop in a central terminus. A review of the routine medical findings indicated that all tests of cardiovascular function had given negative results except the ballistocardiogram, which was severely abnormal and had been reported as suggesting considerable impairment of myocardial function.

Because of this experience about 150 railroad employees have been sent to us for testing. These employees are entrusted with duties, on the proper performance of which the safety of many depends. Those who had a conduction abnormality of some type were sent to us, many of them having right or left bundle branch block as shown by the electrocardiogram. Some had evidence for and a history of heart disease; some were healthy and asymptomatic. The purpose of the study was to determine, if possible, which of them had normal myocardial function and which myocardial abnormality.

Other tests were also performed and our final evaluation has not been made. It soon became evident, however, that the presence of a right or left bundle branch block did not necessarily result in a corresponding delay of the right- or left-sided ballistic events.

Since this experience I have continued to be interested a great deal in the clinical study of cases showing ballistic asynchronism. Starr produced notched J waves in cadavers by injecting fluid into the aorta a little before injecting fluid into the pulmonary artery, and vice versa. Therefore, we have the right to interpret this phenomenon as comparable to asynchronism of the forces developed by the two ventricles. The ultra low frequency records

suggest that a certain amount of such asynchronism may be normal, the right heart tending to eject before the left because of the much lower diastolic pressure in the pulmonary artery than in the aorta. Abnormal degrees of this phenomenon are quite common in patients, and I have been interested in relating it to other phenomena such as bundle branch block and split heart sounds which might be interpreted as indicating ventricular asynchronism or being somehow related to it. When possible in such cases, I secure simultaneous records of heart sounds, electrocardiograms and the pulse waves with the ballistocardiogram, using increased speed of the recording paper. Such records are extremely interesting but conclusions have not been easy to draw. Certainly ballistic asynchronism does not necessarily accompany either split first sounds or bundle branch block. Therefore, my most important conclusion to date is a negative one.

Right bundle branch block is accompanied by an abnormal ballistocardiogram only in a minority of my cases; in the majority the ballistocardiogram is normal in all respects. The electrical abnormality often seems to have no detectable effect on cardiac function and one cannot help but believe that, in such cases, it is of little importance to the patient. On the other hand, left bundle branch block was more often associated with an abnormal ballistocardiogram, although exact figures cannot be given at present. We can say from this group of patients that there was no constant relation between right ballistic delay and right bundle branch block or between left ballistic delay and left bundle branch block. Furthermore, there was no constant relation between right ballistic delay and delay in the tricuspid sound or between left ballistic delay and delay of the mitral sound.

Although perhaps some of these discrepancies are due to deficiencies in the recording technics available to me, physiologic reasons provide ample explanation. The mitral and tricuspid valves close at the onset of the intraventricular pressure rise, and, normally, the maximum acceleration of the blood is also early in systole, so that the sounds coincide with the onset of ballistic deflection in normal patients. However, in a weak heart, while the valves still close at the onset of contraction, the forces may well be delayed, and so the sound precedes the ballistocardiographic deflection.

### HYPERKINESIA

If the ballistocardiogram is unusually large I have sometimes made suggestions for further study to help verify the patient's condition. Thus I have suspected hyperthyroidism in several patients and anemia in others, with confirmation later by the appropriate tests. Other causes of abnormally large ballistocardiograms are, of course, excitement, aortic regurgitation and arteriovenous communications. All these are instances in which the body attempts to compensate for various deficiencies by increasing the cardiac output with more forceful beating of the heart. Let us note that the ballistocardiogram detects only changes in physiologic functions; there is no pattern characteristic of each disease as some seem to expect.

### SUBCLINICAL CARDIAC DECOMPENSATION

Quite often I use the ballistocardiogram to confirm or deny a clinical suspicion of myocardial weakening in the older patient with nonspecific complaints. In such cases the heart size may be normal or only slightly abnormal. The blood pressure and heart rate may also be normal, although the timing and quality of the heart sounds may add to my suspicions. No frank evidence of congestive failure may be evident, and the electrocardiogram is usually of little help. However, in many of these patients the ballistic pattern is definitely abnormal. I often give such patients a trial on digitalis therapy. I can recall many tracings in which an improvement in the ballistic pattern accom panied symptomatic improvement in the patient.

I have three patients whose symptoms of coronary disease were improved after the removal of a diseased gallbladder. This clinical improvement was accompanied by an improved ballistocardiogram.

There are some patients whose ballistocardiographic patterns improve following a definite episode of coronary occlusion with myocardial infarction. I have in mind one case in which the record after an infarction was better than that taken before it. In a man now aged seventy-two, after two single severe episodes of pain presumed to be angina, each attack severe enough to bring him to the hospital, a typical myocardial infarction developed within a year. He was then sixty-eight years of age. Previous to the infarction the ballistocardiogram had shown severe deterioration. Three months after the infarction the ballistocardiogram showed

considerable improvement and eventually returned to practically normal. Coincidentally, his feeling of general health was much improved. He has remained well and is leading a physically active retired life in the country, swimming, fishing, hunting and tramping through the woods. The interest in this case lies in the fact that before the acute episode the ballistocardiogram was more abnormal than it eventually became after it; the return to an almost normal record was accompanied by a better sense of well-being than the patient had had for several years.

### HYPERTENSION

I am intrigued by the physiologic differences indicated by the different kinds of ballistocardiograms found in apparently similar cases of essential hypertension. There is the patient with hypertension whose record is normal; apparently his heart is still competent to eject the blood with the usual snap, despite the increased resistance. Patients are also seen whose ballistic abnormality is a deeply split J wave, and one has the right to believe that the side of the heart opposed by the hypertension can no longer move out the blood with the normal snap, while the other side is able to do so. The most frequent ballistocardiographic pattern observed is that revealing normal H, I and J waves, but showing a very deep K wave with tall diastolic waves. This suggests that while the heart is able to eject blood during systole quite effectively, some physiologic adjustments are occurring during diastole which are not usually appreciated. Finally, patients are seen in whom the ballistocardiogram is small and distorted, the heart being unable to carry on normally in the face of the handicap the increased resistance has added.

Until recently the diastolic pattern of most ballistocardiograms has been so confused with artifacts that an attempt to relate the findings with physiologic events has not seemed worth while. With better records we should now begin to think about it, and large numbers of interesting possibilities present themselves.

When therapy is effective in reducing the blood pressure, the ballistocardiogram may indeed improve greatly and one has ballistocardiographic evidence that the beat of the heart is more forceful. When, despite a fall in blood pressure due to therapy, the ballistocardiogram remains abnormal, I believe that evidence is present suggesting continued cardiac incompetence.

Experience of the type described supports the experience of the astute clinical observer, namely, that measurement of the blood pressure alone is insufficient to evaluate a situation of hypertension. The ballistocardiogram adds information to that given by the blood pressure reading in giving the clinician some impression of how well the heart is handling the increased load imposed by the hypertension. Of particular interest are those patients showing the first two fairly normal patterns described despite extremely high blood pressures in the range of 250/150 mm. Hg. Certain patients reveal the fourth severely abnormal pattern described despite relatively low blood pressures of approximately 170/100 mm. Hg. I find it very difficult not to speculate on the reasons for such unexpected observations. I do believe that in my own hypertensive patients I have a more enlightened viewpoint concerning the cardiovascular status and its prognostic significance gained by information obtained from the ballistocardiogram. For example, the height of the blood pressure is only one factor in the work of the heart. If the blood pressure is doubled, and the cardiac output halved, the heart can support the hypertension without doing more than normal work. When the blood pressure is taken and is found to be high, it is not known that the heart is working harder than normal. It is not more difficult to carry one bucket of water up two flights of stairs than to carry two bucketsful up one flight of stairs.

Similarly, one cannot judge the peripheral resistance with confidence from the height of the blood pressure alone. An abnormally large cardiac output may produce hypertension without a change in caliber of the peripheral vessels. The rises in blood pressure which may accompany emotional tension, excitement, exercise and the action of epinephrine are of this type. Often it can be recognized clinically, and this hypertension is accompanied by a large ballistocardiogram. In patients with essential hypertension ballistocardiograms are either normal or subnormal in amplitude so the distinction between these two general types seems definite.

### AGING

As a final point, let me express my interest in such often discussed conceptions as the aging heart and cardiac fatigue, old terms, but so difficult to detect by the older methods of study that they have been almost meaningless. An example typical of several I have seen was the

ballistocardiogram obtained several years ago from my father at the age of sixty-eight. His tracing was of very small amplitude and of slurred contour. There was little variation in ballistic complex size with phases of respiration. Of particular interest was the finding that a practically normal pattern appeared after exercise. He had played tennis until he was sixty-five and continues to do well at the present time.

## Summary

In this section I have outlined some of my experiences with the ballistocardiogram from a clinical point of view. By citing a few examples I have tried to show how I find the ballistocardiogram useful and stimulating in clinical practice.

By means of the ballistocardiogram I am hopeful that we can use information about the strength and weakness of the hearts of our patients to their advantage in a way which has been hitherto impossible.

If in this paper I have succeeded in adding something to the clinician's understanding of the ballistocardiogram, Dr. Isaac Starr deserves the credit for his careful editing and patient encouragement.

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# Historical Milestones

## Ramazzini on Diseases of Runners and Miners (1713)

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AT THE present time occupational medicine is a flourishing specialty, which is equipped with the full apparatus of conferences, meetings, professorships and periodicals, and which extends its benefits to laboring millions in the more advanced countries of the world. The recent rapid efflorescence of this specialty gives it the appearance of newness, yet in actual fact a classic treatise on general occupational medicine was written as far back as 1700 by Bernardino Ramazzini of Modena and Padua, and treatises on limited parts of the field were written in the sixteenth and seventeenth centuries.

The following excerpts are taken from the 1713 edition of Ramazzini's book "De Morbis Artificum," translated by the late Professor Wilmer Cave Wright under the title "Diseases of Workers" and published in 1940 by the University of Chicago Press under the auspices of the library of the New York Academy of Medicine, which has graciously permitted reprinting of these selections. The footnotes have been omitted.

* * *

### EXCERPTS FROM RAMAZZINI ON DISEASES OF RUNNERS

In bygone times when men practised gymnastics as an art, running was counted with other athletic exercises, not only with a view to gymnastic competitions but also for military purposes. All boys, free-born and slaves, were trained in public gymnasia and taught running by their trainers; and at the games and public shows they ran races, with a garland for the prize. By this sort of training men were made fitter for fighting, and, as Vegetius says: "So that they might charge the foe with all their might, quickly seize strategic positions or forestall the enemy if he planned to take them, and more easily overtake the enemy in retreat." The Turks, with these ends in view, still make use of this admirable military discipline and their troops are drilled in running fast. Plato desired that women also should be trained in running, so that they might help in performing military duties and protecting the homes of their ancestors. According to Suetonius, not only the princes and emperors of Rome but the nobility too had their runners whom they called "footboys." But nowadays training of this sort has gone out of fashion; except that princes and the nobility have servants called "lackeys" whose duty is to run at full speed in front of carriages or travelling-coaches, or on occasion to take a letter somewhere and bring back an answer to their master at top speed.

It follows that men thus employed are afflicted with various maladies. Most of them suffer from hernia and from asthma, an ailment that we very often observe in racehorses; often they become subject to spitting blood. So in Plautus the slave Acanthio, completely exhausted with running too fast and hardly able to breathe, complains to his master: "For your sake I have burst the veins of my lungs; I have been spitting blood for ever so long. . . ."

Also, runners very often incur acute and serious diseases of the chest, e.g. pleurisy and pneumonia, because they are exposed to wind and rain and clad in garments that furnish little protection; they are drenched with sweat, then chilled through, and thus the pores of the skin are stopped up, so that they cannot but be attacked by fatal diseases, especially of the respiratory organs which in running work hardest and

become overheated. Sometimes they burst a small vein in the kidneys and pass bloody urine; for this reason Celsus advises against running if the kidneys are already affected. Runners are very liable to rupture, because the peritoneum bursts or is distended by the pressure of the confined air. Hence Paul of Aegina writes that running must be avoided by those who have buboes or ruptures.

It is certain that in running more air is inhaled than is exhaled, for in order that the strength to keep on running may not give out it is necessary that the air be confined within the thoracic cavity; now when the muscles of the thorax are relaxed by a strong expiration of air, we feel our strength collapse, whereas when the thorax is inflated and the lungs distended, the tonus of the muscles and fibres of the whole body is braced. If, however, we run too violently or too long, since the lungs are completely filled with air, the pulmonary vesicles are inflated and the blood that flows from the right cavity of the heart through the pneumonic blood vessels is abruptly retarded by the contraction and stricture of the ducts; hence ensue ruptures of the blood vessels and spitting of blood, as Galen too observes. For the same reason runners are liable to both primary and secondary, i.e. convulsive, paroxysms of asthma, for acid serum spreads through the intercostal muscles and twitches them with a violent spasm. . . .

These then are the ailments of runners and they aggravate and intensify them by their excess of diet. From ruptures they can easily protect themselves by wearing a truss before they are overtaken by this misfortune, so usual in their case; they can correct emaciation and loss of flesh partly by a moist diet, also by gentle rubbing with oil and taking baths when they can spare the time; by these remedies they will also obviate obstructions of the pores of the skin to which they are exposed after excessive running and sweating. Also by occasional venesection they will ward off ruptures of the blood vessels and spitting blood, and when they are laid up with any serious malady this remedy should certainly not be omitted. For with runners the lungs more than any other organ are overworked and become enfeebled: "Work for the joints, food for the flesh, sleep for the viscera," says Hippocrates. The joints are indeed strengthened by movement and running, just as they are weakened and become sluggish from idleness and leaving off exercise; not so the lungs, for violent running heats them and makes them lose their natural tonus.

These then are the remedies and this the advice that will help to preserve the health of runners; but men of that class never ask a doctor for advice and safeguards unless they are actually laid up in bed or are seized with one of the above-mentioned maladies caused by their task of running. . . .

## Ramazzini on Diseases of Miners

Various and manifold is the harvest of diseases reaped by certain workers from the crafts and trades that they pursue; all the profit that they get is fatal injury to their health. That crop germinates mostly, I think, from two causes. The first and most potent is the harmful character of the materials that they handle, for these emit noxious vapors and very fine particles inimical to human beings and induce particular diseases; the second cause I ascribe to certain violent and irregular motions and unnatural postures of the body, by reason of which the natural structure of the vital machine is so impaired that serious diseases gradually develop therefrom. First, then, I shall give an account of the diseases that arise from the injurious character of the materials; to begin with, those that beset workers in metal or any other craftsmen who employ minerals in their work, such as goldsmiths, alchemists, distillers of aqua fortis, potters, mirrormakers, founders, tinsmiths, painters and others. In the first place, miners know too well what they are like, those noxious pests that lie hidden in the veins of ore; for as they spend all their time in the deepest bowels of the earth they must every day reckon with the god of the underworld. Ovid is right: "Men go down into the bowels of the earth, and what she has hidden away and consigned to the Stygian shades they dig out, wealth, provocative of evils." It is of course obvious that the poet meant evils that corrupt the minds and morals of men and that he desired to denounce the avarice or rather the mad folly of man who has ventured to drag out into the daylight things that we count as "goods," though they are the fount and source of our ills; for as Pliny wisely says: "We have set a price on all that is good." But the poet's words may just as well be applied to the evils that attack men's bodies. Now the diseases to which miners and other workers of that sort are exposed are chiefly dyspnoea, phthisis, apoplexy, paralysis, cachexy, swollen feet, loss of teeth, ulcerated gums, pains in the

joints and palsy. Hence the lungs and brain of that class of workers are badly affected, the lungs especially since they take in with the air mineral spirits and are the first to be keenly aware of injury. Presently, when those vapors have gained entrance to the dwelling-house of life and are mixed with the blood, they pervert and pollute the natural composition of the nervous fluid, and the result is palsy, torpor and the maladies above-mentioned. Hence the mortality of those who dig minerals in mines is very great, and women who marry men of this sort marry again and again. According to Agricola, at the mines in the Carpathian mountains women have been known to marry seven times. Lucretius says of metal miners: "Do you not see and hear that they perish after a brief span and how their vital force fails them?" In the past, and even now where there are mines, mining metals is a regular form of punishment. Malefactors and those guilty of the more serious crimes are condemned to the mines, just as in antiquity the followers of the Christian faith used to be so condemned, as we read in Gallonio on the tortures of the martyrs. . . .

Helmont in his treatise "On Asthma and Cough" describes a kind of asthma which he classifies as something between dry and humid asthma and says that miners and refiners of metals, minters and other such workers are liable to that asthma because of the "metallic gas" that they inhale, which is so powerful that the vessels of the lungs are obstructed. Wedel in his "Pathologia Medica Dogmatica" speaks of "miner's asthma" and says that workers in mines are liable to this ailment; he also says that Stockhausen published a whole treatise on this kind of asthma wherein he ascribed the cause of the malady to mercury of lead; for much mercury is present in lead and makes it heavy. The same author explains how those metallic fumes bring about the cruel monster "miner's asthma" by drying up the bronchia, but this is also caused, he thinks, by their being blocked by sooty smoke. Sennert in his work "On the Agreement and Disagreement of Chemists and Galenists" relates that a doctor whose practice was at the metal mines of Meissen told him that in the corpses of miners had been found the metals that in life they had toiled to dig. . . .

In vitriol mines the miners are usually attacked by respiratory troubles. Galen, in "The Properties of Simple Medicaments," describes a cave that he saw when he was in Cyprus from which water was being carried out by the workmen for making green vitriol and says that he went down into it to a depth of about one-eighth of a mile and observed drops of green water dripping into a pool and was keenly aware of a suffocating and almost intolerable odor. He adds that he saw that the workmen, who were naked, carried out the water with the utmost haste and ran back quickly; nothing, in fact, is worse for the lungs than acid of whatever kind, and in vitriol there is a great deal of acid. I am sure that many of our own clinicians would laugh at any other professor of the natural sciences if they saw him run the risk of descending to explore regions underground so as to investigate the hidden recesses of nature. I know how they laughed me to scorn when I was exploring the sources from which the springs of Modena gush forth, a risky venture, and again when I went down into our petroleum wells situated among the mountains. But let them learn from the example of Galen, who undertook long journeys abroad and with keen curiosity investigated the most secret mysteries of nature in order to learn accurately the virtues of certain medicaments. . . .

So many and so inexplicable are the mixtures of metals confined in the bowels of the earth that it is almost impossible to determine precisely what injurious element is present in this or that mine and how it is that one part rather than another is affected; though, to be sure, the nature and character of the metals and substances mined so far would seem to be thoroughly understood, thanks to the industry of the chemists. Hence we may simply assert in general that confined air when taken in by the mouth for the purpose of respiration, saturated as it is with particles highly injurious to the lungs, brain and spirits, brings about a standstill in the blood mass and the spirits, and lo! a troop of maladies in arms. It will therefore be the duty of superintendents of mines and still more of those who profess the art of medicine and are hired for this very service, to provide as far as may be for the safety of the miners, and whenever it is impossible to remove the exciting cause they must try hard to prevent the men from being injured more than is inevitable. When men of this class fall sick, they ought to be treated in much the same way as are those suffering from incurable diseases, to whom we must not deny medical remedies, at any rate such as have power to alleviate. For as Hippocrates says: "We must study incurable ail-

ments so that they may hurt the patient as little as possible."

In order to purify that imprisoned air infected by the exhalations emitted from the minerals and the bodies of the miners, also by the fumes of lighted lamps, superintendents of mines regularly expel the thick stale air and force in fresh and purer air by means of certain ventilating machines which they connect by shafts with the bottom of the mine. Also they protect the legs and hands of the miners from injury by means of leggings and gloves. It is evident that the ancients also paid great attention to the safety of miners, for, according to Julius Pollux, they used to cover their heads with sacks. Over their faces they tied loose bladders so that they could see through them without inhaling the pernicious dust; Pliny says that this is done by polishers of minium. Nowadays, especially in arsenic mines, they wear glass masks, a safer and neater device mentioned by Kircher.

* * *

## Comments

In studying Ramazzini's text one is immediately impressed by its pleasant, interesting style. In accordance with the habit of the time he ornamented his remarks with allusions or references to the classics, which are always relevant and often serve to lighten or enlighten his material. In the chapter on runners his use of the comic poet Plautus is a deft touch, since Roman comic poetry is full of slaves who are dyspneic from real or feigned haste. Often Ramazzini uses ancient authors, in the typical Renaissance manner, as repositories of illustrative anecdotes. The same trait is observable in Montaigne. At the same time Ramazzini also draws on ancient writings for their technical content, as the quotations from Celsus and Paulus Aegineta indicate. He does not disdain recent authors and does not hesitate to disagree with them. His mention of the Turks and their military methods suggests that Italians—especially northern Italians—still had fresh in mind the memory of their contacts and conflicts with the Levant.

The chapter on runners exhibits a number of curious facts and opinions about the physiology of the circulatory and respiratory systems. Thus Ramazzini says, "It is certain that in running more air is inhaled than is exhaled. . . when the muscles of the thorax are relaxed by a strong expiration of air, we feel our strength collapse, whereas when the thorax is inflated and the lungs distended, the tonus of the muscles and fibres of the whole body is braced (*inflato vero Thorace, Pulmonibusque distentis, musculorum, ac fibrarum totius corporis tonus firmatur*)." Ramazzini was of the opinion that running caused overdistention of the pulmonary vesicles, i.e., alveoli, which compress the pulmonary blood vessels and thus retard the passage of blood from the right heart; this causes rupture of vessels and hemoptysis. A complicating factor, he believed, was the presence of acid serum, which spread through the intercostal muscles and threw them into spasms. Hence runners might develop paroxysms of asthma.

The concept of generalized dyscrasias such as acidosis did not exclude the concept of local lesions, even in the era before Morgagni. Thus Ramazzini reports that runners occasionally suffer from hematuria, which he attributes, without mentioning the evidence, to the rupture of small veins in the kidney.

Ramazzini recognized that the occupational ailments of runners were not caused solely by running. These men suffered incidental exposure to cold and wet, which made them subject to pleurisy and pneumonia. He was well aware that "men of that class never ask a doctor for advice and safeguards unless they are actually laid up in bed or are seized with one of the above-mentioned maladies." In this respect times have changed little.

Ramazzini's chapter on the diseases of miners shows a moralistic tendency. He says that the only profit that miners obtain is fatal injury to their health. Appositely he quotes a familiar passage from Ovid's "Metamorphoses" on the golden, silver, brazen and iron ages; the last-named introduced surveying, navigation, mining and crime.

The discussion of miners' diseases is filled with interesting details. For example, Ramazzini quotes a report of Agricola that mortality among miners in Carpathia was so high that some women in that region married seven times. As is well known, the treatise of Georgius Agricola (1490–1555) was translated from the Latin by Mr. and Mrs. Herbert Hoover. Ramazzini reminds us that work in the mines was used as a punishment for crime; this is documented by reference to a Christian martyrology! This is an example of his wide range of reading, mentioned in a previous paragraph. From Sennert he obtained the fact, known even in these ages of primitive chemistry, that miners' bodies contained some of the minerals they had dug.

The crudity of chemical knowledge at this time is illustrated by Ramazzini's statement that the mixture of metals contained in the earth is so varied and inexplicable that "it is almost impossible to determine precisely what injurious element is present in this or that mine." An analogous crudity is apparent in the medical discussions. Thus the list of diseases is partly a list of symptoms and partly a catalogue of syndromes, e.g., dyspnea, phthisis, apoplexy, paralysis, cachexy, swollen feet and loss of teeth. The concept of individual diseases was yet to emerge clearly.

Ramazzini believed that the lungs of miners became diseased because these workers inhale "mineral spirits," i.e., fumes or sublimates distilled from the minerals and inhaled as gases. These substances mix with the "nervous fluid" which was believed to mediate nerve function. The concept thus was predominantly humoralistic. Ramazzini also believed that the inhalation of noxious substances caused a standstill of the blood and of the spirits.

His interesting study was not limited to description of symptoms and to hypotheses concerning pathogenesis but included also information about preventive measures which were available even at that early date.

The foregoing excerpts and comments necessarily convey nothing more than an incomplete impression of the treasures and pleasures which await the reader of Ramazzini. It is hoped that at least a few of those who see these pages will feel impelled to consult either the original text or Dr. Wright's annotated translation.

# Case Reports

# Primary Pulmonary Hypertension with Death During Right Heart Catheterization

## A Case Report and a Survey of Reported Fatalities*

PAOLO CALDINI, M.D., GOFFREDO G. GENSINI, M.D., F.A.C.C. *and* MURRAY S. HOFFMAN, M.D.

Denver, Colorado

PRIOR TO THE introduction of cardiac catheterization, primary pulmonary hypertension was considered a rare and poorly understood disease. However, during the past two decades, with the almost routine use of cardiac catheterization, there have been many contributions to the literature delineating the clinical picture and course of primary pulmonary hypertension. The natural history of the disease indicated an average life span of from two to five years following the onset of symptoms, although a few patients have lived as long as fifteen years. The afflicted may range in age from infancy to senility, although the disease has a predilection for young adults.

The death of such patients is often preceded by progressively severe right heart failure. More frequently, however, sudden death occurs in a patient who previously had been only slightly or moderately incapacitated by his illness, but who had increasingly severe and frequent syncopal attacks. Sudden death may occur during or immediately following special investigative procedures. The concept has thus arisen of the fragility of the patient with primary pulmonary hypertension and the hazard of any diagnostic or operative procedure in such a case.

It is the purpose of this paper to present the history of a patient with primary pulmonary hypertension who died during cardiac catheterization, while the pressures were being recorded in the right heart and while a continuous electrocardiogram was being obtained. Therefore, it was possible to observe the mode of death in a patient with this disease, as well as to assess the potential hazards of right heart catheterization.

### CASE REPORT

C. W. A., a twenty-three year old white married man, was admitted to the National Jewish Hospital on January 23, 1958. The patient was born of a normal pregnancy and full term spontaneous delivery; however, he was said to be "blue from the waist down" during the first hours of life. This condition subsequently disappeared, never to return again. Growth and development were normal. The patient enjoyed an apparently normal, healthy life. In 1952 a diagnosis of a duodenal ulcer was made by x-ray examination. His symptoms, however, improved following adequate medical treatment.

In May 1955, at age twenty-two, the patient experienced his first episode of syncope while working in a bakery, hurrying and in a hot environment. He recovered after a few minutes, and experienced no further symptoms for the next several months. In September 1957, his second episode of syncope occurred while he was playing baseball. Examination of the heart at this time was said to show no abnormalities. However, in October 1957, the patient was first noted to have a heart murmur. Approximately six months prior to admission he noted increasing limitation in physical activity because of exertional dyspnea. He had no episodes of orthopnea or paroxysmal nocturnal dyspnea. The patient had noted pitting edema a few weeks prior to admission and concomitantly experienced a sensation of heaviness in the right upper quadrant of the abdomen, not related to food ingestion or to exercise.

*Physical Examination:* Examination revealed a well

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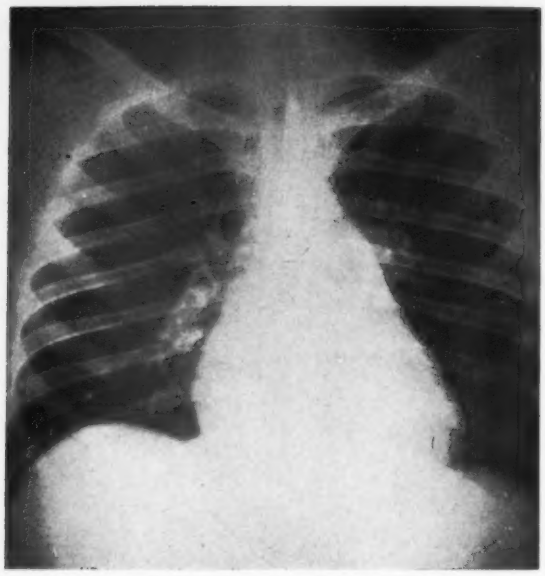

FIG. 1. Roentgenogram of the chest, posteroanterior view.

developed, well nourished white male, age twenty-three, in no acute distress. Height was 5 feet, $10^1/_2$ inches, weight 156 pounds. Temperature was 98.4°F. Repsirations were 24 per minute. No cyanosis, edema or dyspnea were observed. There was a suggestion of hippocratic fingers on both hands; however, no definite clubbing was present. The liver was palpable 4 cm. below the right costal margin in the mid-clavicular line and 10 cm. below the xiphoid process. The lungs were clear. The remainder of the general examination revealed no abnormalities. The radial pulse was of small amplitude, with 110 beats per minute. Femoral pulsations were also small. Blood pressure was 100/90 mm. Hg in both arms. Neck veins were slightly distended and revealed prominent A waves.

The precordium was normally active on inspection, with a distinct right ventricular thrust present along the left sternal border. Over-all size of the heart appeared to be moderately enlarged on percussion. The point of maximal impulse was felt in the fifth interspace along the mid-clavicular line. A shock-like sensation coincident with pulmonic valve closure was felt at the second left interspace. No thrills were palpable. On auscultation, a pulmonic systolic click was audible in early systole in the second left interspace. $P_2$ was markedly accentuated, although not definitely split. A grade 2, high-pitched, blowing, systolic murmur was heard along the lower left sternal border This murmur occupied all of systole. The intensity of the murmur

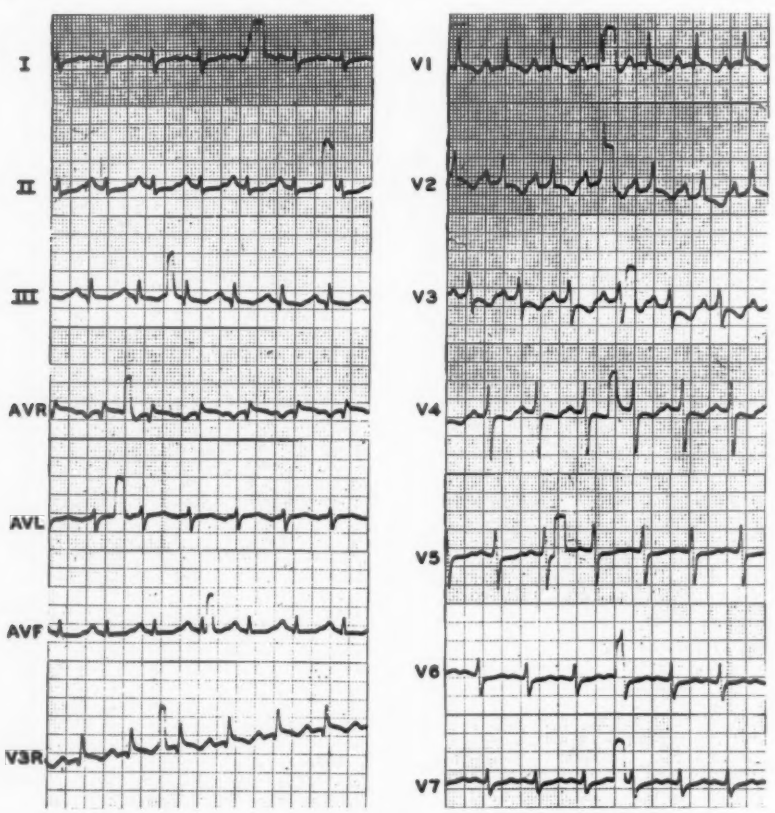


FIG. 2. Electrocardiogram taken shortly after admission.

was increased with inspiration. In this same area a presystolic gallop sound was heard.

*Laboratory Findings on Admission:* Hemoglobin was 17.5 gm. per cent, red blood count 6,250,000 per cu. mm.; hematocrit 55 per cent; white blood count 10,500 per cu. mm., with 66 per cent polynuclear cells, 33 per cent lymphocytes and 1 per cent monocytes. Sedimentation rate was 1 mm. in sixty minutes. Urinalysis revealed the specific gravity to be 1.015, reaction 5, negative for sugar and acetone, although containing a trace of albumin. Microscopic examination of the urine revealed occasional white blood cells per high-power field. Fasting blood sugar was 95 mg. per cent; blood urea nitrogen, 15 mg. per cent; total protein, 7.2 gm. per cent; albumin, 4.2 gm. per cent; globulin, 3 gm. per cent; sodium, 139 mEq./L.; chloride, 100 mEq./L.

X-ray and fluoroscopic examination (Fig. 1) revealed the over-all size of the heart to be considerably increased. Main, left and right pulmonary arteries were markedly enlarged and exhibited increased amplitude of pulsations. Peripheral lung vascularity was abnormally clear. The right ventricle was definitely enlarged, as was the right atrium. The left ventricle and left atrium appeared normal. The ascending aorta appeared somewhat prominent. The electrocardiogram revealed right ventricular hypertrophy (Fig. 2).

*Hospital Course:* Since the patient was believed to be in minimal right heart failure on admission, he was placed on a low salt diet and given digitalis. Within forty-eight hours following admission, his neck veins and liver were somewhat less prominent. On the third day of hospitalization, the patient was found unconscious in bed in a state of peripheral vascular collapse. Historically, this then constituted his third syncopal attack. He recovered with the use of vasopressor drugs and subsequently appeared well without apparent sequelae.

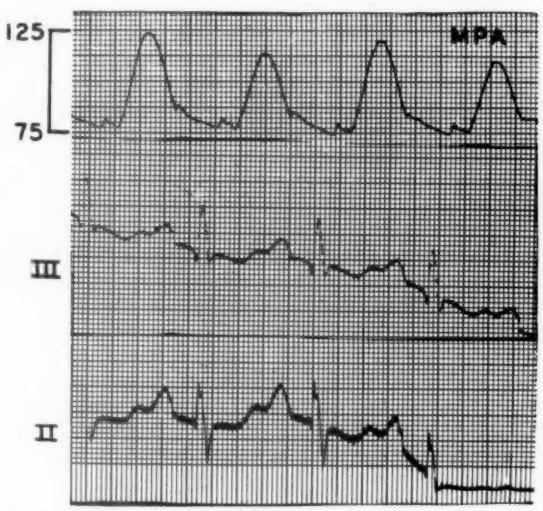


FIG. 3. *Upper tracing*, pulmonary artery pressure tracing obtained during cardiac catheterization, before the first syncopal attack, averaging 125/75 mm. Hg. *Lower tracing*, leads III and II of the electrocardiogram recorded at the same time.

FIG. 4. Pulmonary artery pressure recorded during the syncopal seizure, showing a mean value of 55 mm. Hg. The lead II of the electrocardiogram reveals complete A-V block with marked depression of the S-T segments.

*Right Heart Catheterization:* On January 28, 1958, the patient was admitted to the Cardiopulmonary Laboratory for right heart catheterization. Following preparation with prophylactic penicillin, and under local anesthesia, a skin incision was made in the left antecubital space, the medial basilic vein thus being isolated. The vein admitted a No. 7 Cournand catheter which was advanced via the superior vena cava into the right atrium. The right ventricle, and the main and right pulmonary arteries were then readily entered without appreciable manipulation. The continuous oscilloscopic monitoring of the electrocardiogram did not reveal any abnormality of the rhythm during the procedure thus far.

The right ventricular and right pulmonary artery pressures were recorded and found to be 135/0 and 125/75 mm. Hg, respectively (Fig. 3). A blood sample collected from the main pulmonary artery revealed an oxygen saturation of only 23.5 per cent.

While the expired air was being collected in a Douglas bag, the patient went abruptly into an attack characterized by dyspnea, loss of consciousness, generalized muscular contraction, absent peripheral pulses, coldness, clamminess and cyanosis. The collection of air was immediately discontinued. The mean pulmonary artery pressure recorded during the attack was 55 mm. Hg, with virtually no pulse pressure (Fig. 4). When the convulsive seizures began to subside, it was possible to record a legible electrocardiogram. It was evident that the patient had a complete A-V block (Fig. 4) with a ventricular rate of 70 beats per minute, P waves being present at a frequency of 120 per minute. Marked depression of S-T segments were observed in multiple leads.

This syncopal attack lasted about forty seconds, after which the patient spontaneously recovered. The pressure in the pulmonary artery at this time was recorded as being 86/28 mm. Hg. However, in spite of now good pulmonary pulse pressure, no significant changes occurred in the electrocardio-

FIG. 5. Pulmonary artery pressure recorded immediately after the recovery, averaging 86/28 mm. Hg. Complete A-V block in lead II of the electrocardiogram. The marked S-T segment depression has disappeared.

gram, the A-V block persisting with a ventricular rate of 50 and atrial rate of 100 per minute (Fig. 5).

After approximately another half minute, the patient suffered another similar syncopal attack. The catheter was now quickly withdrawn and the usual maneuvers of resuscitation instituted, including mouth-to-mouth breathing, cardiac massage, vasopressors, etc. These were, unfortunately, without success and the patient was pronounced dead thirty minutes later.

*Autopsy:* With the exception of chronic passive congestion of the abdominal viscera, abnormalities were restricted to the heart and lungs. The heart weighed 510 gm. The epicardium showed petechial hemorrhages. The right chambers were disproportionately enlarged and dilated. The right ventricular wall measured up to 8 mm. thick, and the trabeculae were prominently enlarged. The left ventricle was contracted, and the wall measured 12 mm. thick. The valves were all thin, flexible and smooth. The tricuspid valve measured 16 cm. in circumference, the pulmonic valve 8.5 cm., the mitral valve 12 cm. and the aortic valve 6.5 cm. Mural thrombi and congenital anomalies were absent. Microscopically, the myofibers of the right ventricle were particularly hypertrophic; the coronary arteries and the aorta appeared to be normal.

The right and left lungs weighed 465 gm. and 425 gm., respectively. The pleura was thin and smooth. Vascular dilation, arterial thrombi and distinct intimal atheromas were not observed. The parenchyma of the right lung was soft, pink and crepitant. The left lung exhibited complete collapse. The bronchi were patent. The hilar lymph nodes were not noteworthy.

Microscopically, a striking alteration involved all the pulmonary arteries, particularly the medium-sized and small muscular vessels. The media was hypertrophic and richly nucleated, and the intima was thickened with collagenic tissue. The smallest arteries frequently exhibited obliteration of the lumen with fibrillary collagen and with proliferated endothelial nuclei (Fig. 6). A few polymorphonuclear cells occasionally were present in the adventitia. Recent thrombus formation was not observed,

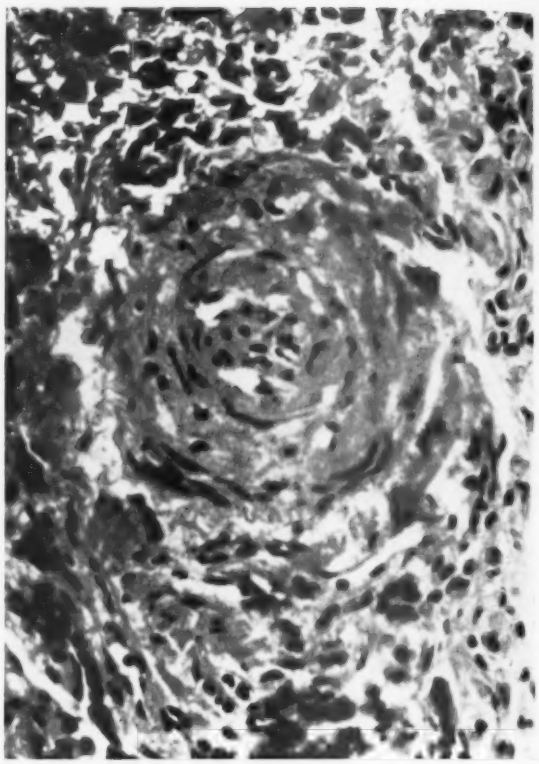

FIG. 6. Small pulmonary muscular artery exhibiting thickened wall and obstruction with connective tissue. (Hematoxylin and eosin × 200.)

although one small artery contained congealed erythrocytes. The large elastic arteries exhibited a moderate, diffuse increase of fibrocellular intimal tissue with superficially located mononuclear cells and foam cells. The arterioles had thin walls, and the alveolar septa were delicate. Small patches of hemosiderin cells were present in the alveoli. The left lung, in addition, exhibited collapse and edema.

## COMMENTS

Two pertinent questions might be raised in this case: (1) What was the relation between heart catheterization and death? and (2) What are the physiologic mechanisms underlying syncope in the patient with primary pulmonary hypertension?

Bagger and associates[1] collected 5,859 cases of right heart catheterization. The total number of such procedures that have been performed to this date throughout the world is probably in the tens of thousands. In experienced hands the procedure has been found to be generally quite harmless and virtually indispensable in evaluation of the pathophysiology of cardiopulmonary disease. However, potential hazards

TABLE I

Fatalities Due to Arrhythmias and Related to Cardiac Catheterization

| Case No., Sex and Age (yr.) | Author and Year of Report | Diagnosis | Time of Death | Events Leading to Death | Cause of Death | Autopsy Data |
|---|---|---|---|---|---|---|
| 1 | McMichael,[2] 1948 | Coronary artery disease | During catheterization | Runs of premature ventricular contractions | Ventricular fibrillation | ..... |
| 2 | Wood,[3] 1950 | Congestive heart failure | During catheterization | ..... | Ventricular fibrillation | ..... |
| 3, F, 10 | Goldman et al.,[4] 1950 | Paroxysmal tachycardia with congestive failure | Catheter tip in right ventricular outflow tract | Ventricular tachycardia 180/min. | Ventricular fibrillation | Extensive myocardial and endocardial scarring of left ventricle and septum; rhabdomyoma of the myocardium; tricuspid insufficiency |
| 4 | Cournand et al.,[5] 1951 | Pulmonary hypertension | Catheter tip in right ventricle | During exercise | Cardiac standstill | ..... |
| 5 | Cournand et al.,[6] 1953 | Silicosis | During catheterization | During strenuous exercise, severe tachycardia | Cardiac standstill | Autopsy negative for fresh lesions |
| 6, M, 34 | Edwards et al.,[7] 1953 | Ventricular septal defect; pulmonary hypertension; patent ductus arteriosus; mitral disease | During catheterization | ..... | Ventricular fibrillation | Ventricular septal defect; patent ductus arteriosus; mitral insufficiency |
| 7, 2 | Ziegler,[8] 1954 | Severe pulmonary valvular stenosis; congestive heart failure | ..... | ..... | Ventricular fibrillation | ..... |
| 8 | Margulies and Gustafson,[9] 1955 | ..... | During catheterization | ..... | Ventricular fibrillation | ..... |
| 9, F, 8 | Kjellberg et al.,[10] 1955 | Fallot's tetralogy | 24 hr. after catheterization | Ventricular tachycardia; poor general condition | Heart failure | ..... |
| 10, F, 10 | Haeger et al.,[11] 1955 | Eisenmenger complex; persistent left superior vena cava | Catheter tip at junction of left innominate vein with left jugular vein | Vomited; respiratory standstill | Cardiac standstill | Confirmed clinical diagnosis; hemorrhagic lesion around the vascular junction and the vagus |
| 11, M, 1 | Berthrong and Cochran,[12] 1955 | Ebstein's disease | Shortly after catheterization | ..... | Cardiac standstill | Primary pulmonary hypertension |
| 12, M, 14 | Schafer et al.,[13] 1956 | Primary pulmonary hypertension | End of catheterization | Nausea, convulsion, unconsciousness, sinus tachycardia, A-V block, ventricular standstill | Cardiac standstill | Primary pulmonary hypertension |
| 13, F, 9 | Schafer et al.[13] 1956 | Primary pulmonary hypertension | End of catheterization | Nausea, vomiting, unconsciousness, A-V block | Cardiac standstill | ..... |
| 14, M, 33 | Schafer et al.,[13] 1956 | Ventricular septal defect; pulmonary insufficiency | End of catheterization | Ventricular tachycardia | Ventricular fibrillation | Primary pulmonary hypertension |
| 15, M, 60 | Bagger et al.,[1] 1957 | Arterial hypertension; left bundle branch block | Catheter tip in right atrium | ..... | Cardiac standstill | ..... |
| 16, M, 52 | Bagger et al.,[1] 1957 | Aortic stenosis | Catheter tip in right ventricle | ..... | Cardiac standstill | Fresh myocardial infarct |

are present and fatalities have been described. The low risk of this procedure, however, may be seen from the fact that this represents the first cardiac catheterization in which there was any suggestion that the procedure contributed to a fatality in a series of 1,000 cardiac catheterizations performed by one of the authors (G. G. G.).

TABLE II
Fatalities Related to Gross Anatomic Lesions Attributable to Cardiac Catheterization

| Case No., Sex and Age (yr.) | Author and Year of Report | Diagnosis | Time of Death | Events Leading to Death | Cause of Death | Autopsy Data |
|---|---|---|---|---|---|---|
| 1 | Johnson et al.,[14] 1947 | ..... | 1 mo. after catheterization | ..... | Heart failure | Thrombus in right atrium, inferior vena cava, iliac and renal veins |
| 2, M, 17 | Baker et al.,[15] 1950 | Ebstein's disease | 2 wk. after catheterization | Bilateral gangrene of legs 1 wk. after catheterization | Heart failure | Partially organized thrombi in septal wall, left ventricle, which catheter entered via atrial septal defect |
| 3 | Cournand et al.,[6] 1953 | Mitral insufficiency | 2 hr. after catheterization | Sudden pain at precordium | ... | Subendocardial necrosis in outflow tract of right ventricle |
| 4, M, 44 | Goodwin,[16] 1953 | Mitral stenosis; aortic stenosis; pulmonary hypertension | Catheter tip in right ventricular outflow tract | Shock; blood pressure 90 mm. Hg; cardiac pain; ECG, pericarditis | Circulatory failure | Small area of necrosis, anterior wall of right ventricle close to left coronary artery |
| 5, F, 33 | Nightingale and Williams,[17] 1955 | Mitral stenosis; auricular fibrillation; congestive heart failure | 3 wk. after catheterization following commissurotomy | Catheter kept in wedge position in right pulmonary artery for 29 min. | Respiratory death in postoperative period | Thrombosis of right main branch of pulmonary artery |
| 6, F, 37 | Svedberg and Storer,[18] 1958 | Mitral stenosis and left intra-atrial mass | 9 hr. after catheterization | Chill, dyspnea; pulmonary edema at end of catheterization with catheter inside heart | Heart failure | Thrombus in right atrium and right pulmonary artery; myxoma of left atrium; mitral stenosis |
| 7, F, 10 | Peel et al.,[19] 1956 | Cyanotic congenital heart disease | During catheterization | Cyanosis localized in left side of face and left arm; respiratory insufficiency | Cerebral anoxia | Left superior vena cava entering left atrium; patent ductus arteriosus |

At first glance it would appear that the case herein reported represents a clear-cut example of a fatality due to right heart catheterization. However, further analysis is necessary. Considering the large number of cardiac catheterizations performed to this date, and the high inherent mortality of the population undergoing catheterization, it seems possible that death and heart catheterization might coincide in some patients and one not really be related to the other.

## RELATION OF CARDIAC CATHETERIZATION AND SUDDEN DEATH

This hypothesis is supported by a close analysis of the cases of death associated with heart catheterization reported in the literature.[1–21] In many of these patients, of course, heart catheterization clearly was the cause of death. In others, the relationship is very vague. In Tables I, II and III, the fatalities associated with cardiac catheterization reported in the literature during the past ten years are reviewed. A number of cases are reported as personal communications, and an accurate description of these deaths is not available. The total number of reported fatalities occurring during cardiac catheterization, or shortly thereafter, appears to be thirty-one. It is reasonable to assume that the total number of deaths associated with cardiac catheterization is surely higher than the number reported in the literature. The thirty-one cases we have collected can be divided into three main groups according to the events occurring at the time of catheterization and the cause of death given by the different authors.

*Deaths Attributed to Arrhythmias:* The largest group is definitely that of fatalities due to arrhythmias (Table I). It is comprised of sixteen patients. Ventricular fibrillation is described as the cause of death in seven patients, and cardiac arrest in eight patients. In one patient a ventricular tachycardia occurred at the time of cardiac catheterization leading to heart failure and death twenty-four hours later. In this group pathologic examination did not show

TABLE III
Fatalities Questionably Related to Cardiac Catheterization

| Case No. and Age | Author and Year of Report | Diagnosis | Time of Death | Events Leading to Death | Cause of Death |
|---|---|---|---|---|---|
| 1, 7 mo. | Michel et al.,[26] 1950 | Transposition of great vessels and foramen ovale; small ventricular septal defect | Following thiopental sodium anesthesia and introduction of catheter into venous tree | Series of varied arrhythmias | Respiratory failure; cardiac standstill |
| 2, Elderly | McMichael, cited by Zimdahl,[21] 1951 | Severe coronary artery disease | During catheterization | Ventricular tachycardia following full dose of digitoxin | Digitalis death |
| 3 | Cournand et al.,[6] 1953 | ..... | During preparation for cardiac catheterization | ..... | ..... |
| 4, 11 wk. | Ziegler,[8] 1954 | Cyanotic congenital heart disease | During preparation for cardiac catheterization | Anoxia | Anesthetic death |
| 5, 3 yr. | Ziegler,[8] 1954 | Primary pulmonary hypertension | During preparation for cardiac catheterization | Respiratory depression | Anesthetic death |
| 6, 34 yr. | Ziegler,[8] 1954 | Mitral and aortic rheumatic disease; severe heart failure | Immediately after catheterization | Fever, chill and collapse | Heart failure |
| 7, 3½ yr. | Ziegler,[8] 1954 | Coarctation of aorta, mitral atresia | ..... | ..... | Heart failure |

esions that could be attributed to direct injury produced by the catheter, with two possible exceptions: one patient in whom a hemorrhagic lesion was found around the junction of the left superior vena cava and the left subclavian vein, and another in whom a fresh myocardial infarction was found sometime after right heart catheterization. Some of the deaths in this group might well have been coincidental.

*Deaths Related to Direct Trauma:* In the second group the fatalities are related to gross anatomic lesions, presumably produced by the traumatic action of the catheter (Table II). This group is comprised of seven patients. In two there was a small area of necrosis of the wall of the right ventricle, whereas in four other cases there was a thrombus either in the cavity of the right heart or in the main pulmonary artery. The relationship of catheterization to death seems better established in this group. In the seventh case death was explained on the basis of cerebral anoxia produced by spastic occlusion of the left superior vena cava, induced by the catheter.

*Probably Unrelated Deaths:* A third group of deaths (Table III) includes patients who died at the time of cardiac catheterization but in whom the sequence of events or the mechanism of death demonstrated that the introduction of a cardiac catheter was not directly responsible for the fatal outcome.

It is noteworthy that in the first group of deaths due to catheterization there were seven patients with primary pulmonary hypertension which was either suspected clinically or established at the time of necropsy. Two of these patients[13] exhibited symptoms at the time of death that were rather similar to our patient's. It is also interesting to note that all the patients in this group had extremely severe cardiac disease. In addition to the seven patients with pulmonary hypertension, there were three patients who were in congestive heart failure at the time of catheterization. In addition, one patient had coronary artery disease, one had arterial hypertension and left bundle branch block, one had aortic stenosis, and one had severe tetralogy of Fallot. Thus it is seen that many of the so-called "catheterization deaths" occur in extremely ill patients.

*Causes of Death in Primary Pulmonary Hypertension:* Considering that the patient described in this report was proved to have primary pulmonary hypertension, it may be interesting to analyze the types of deaths in the patients with primary pulmonary hypertension reported in the literature.

Berthrong and Cochran[12] reported nine cases of pulmonary hypertension in children; five of these patients died suddenly. It may be worth mentioning that one of these patients died at the moment of injection of the contrast medium for angiocardiography and another died with sudden cardiac arrest shortly after catheterization had been performed.

The lability of patients with primary pulmonary hypertension is well known. In an un-

published article by Blount and Arrington,[22] one of their patients with primary pulmonary hypertension was scheduled for cardiac catheterization, left the hospital against medical advice and died at home at approximately the same time that catheterization had been planned.

### MECHANISM OF SYNCOPE IN PRIMARY PULMONARY HYPERTENSION

Syncopal seizures are outstanding features in primary pulmonary hypertension. The mechanism of the syncopal attack in the presence of pulmonary hypertension is still not completely understood. However, since the typical hemodynamic features of primary pulmonary hypertension are high pulmonary artery pressure, high pulmonary vascular resistance and low cardiac output, it would seem logical that a further, even slight reduction of a critically low cardiac output would become an important link in the chain of events leading to the syncopal attack, and could produce sudden death in these patients.[23–26]

Howarth and Lowe[23] recorded continuous right ventricular and systemic pressures during attacks of unconsciousness deliberately produced by effort in a patient with primary pulmonary hypertension. These authors showed that following exercise the pulmonary vascular resistance rose, accompanied by a fall in systemic pressure, leading to unconsciousness. The authors concluded that right heart failure with diminishing cardiac output was the cause of the falling systemic blood pressure. A steep rise in pulmonary arterial pressure, found on exercise, appears to be secondary to the increase in pulmonary vascular resistance. However, the cause of this sudden further rise of pulmonary vascular resistance remains incompletely explained. A few mechanisms can be speculated upon in explanation of this phenomenon. The extremely low oxygen saturation of the pulmonary artery blood sample, taken just before the attack, as in our case, may suggest hypoxia as a possible factor. Of course, humoral and nervous regulation of pulmonary vasculature, mechanisms which are poorly understood at the present time, may also be considered.

It is believed that the case reported herein is a rather typical example of the sequence of events that takes place in sudden death in primary pulmonary hypertension. A pulmonary artery pressure of 125/85 mm. Hg in the face of pulmonary artery oxygen saturation of 23.5 per cent would indicate that the cardiac output at that time was extremely low. Any further, even minor, increase in pulmonary vascular resistance would reduce the cardiac output to such an extent that cerebral oxygen requirements would not be met, thus explaining the convulsive seizures. That myocardial hypoxia was induced in this patient at the same time was inferred by finding marked depression of the S-T segment and inversion of the T waves in leads II and III. This hypoxia produced the A-V block and further decreased the cardiac output.

It is believed that the A-V block was not the cause of the syncopal seizure but an effect of the acute right ventricular failure, which failure also produced the pulseless pulmonary arterial pressure recorded at this time.

Thus, it seems fair to conclude that a minor increase in pulmonary vascular resistance of unknown origin set in motion a chain of events that led to the death of this patient.

## SUMMARY

Observations regarding the death of a patient with primary pulmonary hypertension during right heart catheterization are reported. After the succession of events in this case is considered, and the literature concerning fatal outcomes during cardiac catheterization reviewed, it is concluded that cardiac catheterization could well have been unrelated to the death of the patient. It is possible, however, that the psychologic distress and the minimal hemodynamic derangement inherent in catheterization can increase pulmonary vascular resistance and lower cardiac output to an extent that would cause a syncopal attack and sudden death in a patient with this disorder.

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# Idiopathic Cardiomegaly with Extreme Cardiac Enlargement

## Hypoplastic Aorta as Primary or Secondary Factor?*

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A NINETEEN year old man with heart disease of obscure etiology, who weighed 142 pounds and measured 72 inches in height, was found at autopsy to have a heart weighing 1,300 gm. Cardiac hypertrophy to this extreme degree is uncommon.

The largest heart on record was mentioned by Sedgwick[1] in 1854. He referred to a heart in the museum of St. George's Hospital which was "said to weigh five pounds." According to Golden and Brams[2] in 1937, an inquiry about this specimen revealed that it had been lost together with all information concerning it. In a review of the literature of the previous century these same authors[2] found reports of only thirty-eight hearts weighing over 1,000 gm. The largest of these was reported by Stokes in 1869 to weigh 1,980 gm. Golden and Brams added nine cases of their own in which the heart weighed in excess of 1,000 gm. These were collected over an eight-year period. The largest weighed 1,475 gm. and was reported as a case of idiopathic cardiac hypertrophy. Cabot[3] studied 1,906 cases of cardiovascular disease found among the 4,000 autopsies performed at the Massachusetts General Hospital between 1896 and 1919. Only seven hearts were found to exceed 1,000 gm. in weight. The largest weighed 1,328 gm. and demonstrated chronic pericarditis with mediastinitis. Evans and White[4] found only five hearts weighing 900 gm. or more among 2,000 consecutive autopsies performed at the Massachusetts General Hospital between May 1941 and April 1946. The largest weighed 1,350 gm. and was due to isolated mitral valve deformity.

The most common causes of massive hypertrophy of the heart are hypertension,[4,5] and valvular deformity.[2-5] Less common causes include coronary sclerosis, obesity, syphilitic aortitis with aortic insufficiency and atrial septal defect, each of which were reported by Rosenow and Smith[5] to produce hearts weighing 800 gm. or more. Hearts weighing in excess of 1,000 gm. are also sometimes seen in familial cardiomegaly.[6,7] The heart in persons with acromegaly may exceed 1,000 gm. in weight,[8] and Epstein[9] recently reported a 1,340 gm. heart in a patient with rheumatic aortic endocarditis and acromegaly.

### CASE REPORT

This nineteen year old white male was admitted to the University of Kansas Medical Center for the first time on April 17, 1958, with the chief complaint of having had "fainting spells" since August 1957.

The patient was born of an uneventful pregnancy. A few days after birth he had an episode of cyanosis apparently lasting only a few minutes but had never been cyanotic since. Throughout elementary school he had an average exercise tolerance. During the first year of high school he noted that he was becoming more short of breath than others during athletic events. At this time he was told for the first time that he had a heart murmur. During his first year at college in the fall of 1956 he participated in ROTC and intramural sports but was more short of breath than others.

In May 1957 he began working as a postal clerk handling mail bags. In August 1957 he began having episodes of syncope, the first of which occurred at work. These were of sudden onset but were usually preceded by a "funny feeling." They were not associated with convulsions, tongue biting or

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fecal or urinary incontinence. The periods of unconsciousness never exceeded one minute. They occurred at a frequency of from one to five per week. In August 1957 he was studied at the University of Colorado School of Medicine. This study included cardiac catheterization. A diagnosis of heart disease of undetermined etiology was made at that time. About one month prior to this admission his episodes of syncope began to grow progressively more frequent and during the two days prior to admission they occurred as often as every five to ten minutes.

The review of systems and past history showed no abnormalities except as noted previously. The family history revealed his parents, four sisters and one brother to be in good health. Two other sisters were known to have heart murmurs (*infra vide*).

*Physical Examination:* This revealed a mildly apprehensive white male who weighed 142 pounds and was 72 inches in height. The patient was in no distress at the time of admission. Blood pressure was 115/10 mm. Hg, apical pulse 28 and respirations 48 and regular. There were no enlarged lymph nodes, the neck was supple, the thyroid was not enlarged and the carotid arteries were pulsatile bilaterally. The left anterior side of the chest was more prominent than the right. The lungs were clear. The apex beat was in the sixth interspace in the anterior axillary line. The heart rate was regular at 28 per minute. A grade 2 systolic murmur was heard along the left sternal border. A grade 1 diastolic rumble was present at the third interspace along the left sternal border. The sounds of atrial beats could be heard. Examination of the abdomen was non-contributory. The extremities revealed the femoral pulses to be of normal volume bilaterally and no edema was present. The neurologic examination was within normal limits.

*Laboratory Findings:* The urine revealed a specific gravity of 1.011, an acid reaction, a trace of albumin and a negative result in the test for sugar; the sediment contained 5 to 8 white cells, occasional red cells and red cell clumps, occasional disintegrated pus casts and a few bacteria per high-power field. The blood count revealed a hemoglobin of 13.3 gm. per cent and a white cell count of 11,650 per cu. mm. The differential count was: neutrophils, 84; lymphocytes, 8; and monocytes, 8. The platelet count was 176,000 per cu. mm. and the hematocrit was 42 per cent. The reticulocyte count was 2 per cent. The sedimentation rate was 5 mm. in 1 hour (Cutler). The serologic test for syphilis was non-reactive. Blood urea nitrogen was 18 mg., the two-hour postprandial blood sugar 80 mg., serum albumin 4.0 gm., serum globulin 2.75 gm., cholesterol 123 mg., cholesterol esters 65 mg., total bilirubin 0.4 mg. and direct bilirubin 0.1 mg. per 100 ml. The serum sodium was 139 mEq., potassium 4.9 mEq., chlorides 103 mEq., calcium 5.2 mEq., phosphorus 2.5 mEq. and carbon dioxide 25.2 mEq. per L. The alkaline phosphatase was 1.5 mm. units and the thymol turbidity 1 unit. The cephalin flocculation test gave a negative result. The venous pressure was 7.5 cm. of saline, the Decholin® circulation time twenty seconds and the ether circulation time eight and a half seconds.

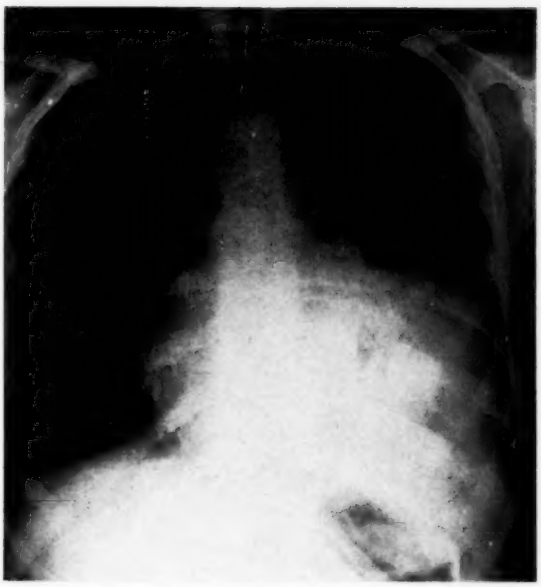

FIG. 1. X-ray film of chest indicating size of heart.

X-ray and fluoroscopic examination of the chest (Fig. 1) revealed the transverse diameter of the heart to be 21 cm. Both ventricles were greatly enlarged. The main pulmonary segment was slightly enlarged. The right pulmonary artery revealed moderately increased pulsation. The left ventricular clearance angle was 90 degrees. The lung fields were clear. The electrocardiogram revealed complete atrioventricular dissociation with an idioventricular pacemaker. The P waves in lead II had a tall peaked appearance. The results of cardiac catheterization carried out at the University of Colorado by Dr. S. Gilbert Blount, Jr. in August 1957 were obtained. The cardiac output was 2.65 L. per minute at rest and 2.89 L. per minute during exercise. The A-V oxygen difference was 6.23 vol. per cent at rest and 12.28 vol. per cent following exercise. The procedure indicated otherwise normal results. An electrocardiogram recorded in August 1957 was obtained and showed first degree A-V block and a QRS duration of 0.20 second.

*Clinical Course:* On admission to the hospital the patient was in no distress and was ambulatory. However, on the evening of his first hospital day he began having repeated episodes of prolonged ventricular standstill associated with unconsciousness and generalized clonic muscular contractions. These lasted as long as three minutes. During one prolonged episode atrial dissociation was demonstrated in his electrocardiogram. The report on this

FIG. 2. Section through the left ventricle demonstrating the thickness of the ventricular wall.

FIG. 3. Cross sections of the mid-thoracic aorta. Note the small caliber relative to the thumb and centimeter rule.

electrocardiogram has been submitted for publication elsewhere.[10] He was connected to a cardiac monitor-pacemaker throughout the remainder of his hospital stay. His hospital course was characterized by attacks of ventricular standstill which varied from single brief episodes of a few seconds' duration to repeated episodes of several hours' duration, during which time spontaneous ventricular contraction did not occur and prolonged interrupted stimulation from the cardiac pacemaker was necessary to maintain the cardiac output.

Numerous medications were used in attempting to prevent or terminate these episodes, including epinephrine intramuscularly and by intravenous drip; isoproterenol hydrochloride sublingually and by intravenous drip; sodium lactate orally and by intravenous drip (1 molar solution); hydrocortisone by intravenous drip; prednisone and digitoxin orally. At no time was atrioventricular conduction re-established. At times intravenous epinephrine, isoproterenol or molar lactate seemed effective in terminating or preventing episodes of ventricular standstill but at other times were totally ineffective. Intravenous epinephrine was given at rates up to 64 μg. per minute and in total doses up to 32 mg. per twenty-four hours. Isoproterenol was given at rates up to 12 μg. per minute and in total doses up to 7 mg. per twenty-four hours. Intravenous molar lactate was given in doses up to 2,510 mEq. of sodium lactate in an eight-hour period. Brief runs of ventricular tachycardia frequently developed when the patient was given intravenous epinephrine at high rates of flow. It was often noted that prolonged or repeated episodes of ventricular standstill were more prone to develop when he became apprehensive. On several occasions when he was having repeated episodes of ventricular standstill with associated thrashing about of his arms, the intravenous solutions extravasated. This often produced severe pain. On three occasions when meperidine hydrochloride was given it was noted that within a few minutes the patient went to sleep and his episodes of ventricular standstill ceased. This was attributed to the sedative effect of the meperidine and it was decided to sedate the patient. He was given 400 mg. of meprobamate every four hours. During the succeeding week he had only two brief episodes of asystole and was discharged to the care of his private physician on June 1, 1958.

The patient did fairly well at home with only occasional episodes of syncope for one month. A cough, shortness of breath and chest pain then developed which grew progressively worse over a three-day period. He died in the emergency room of the local hospital. Autopsy was performed by Drs. J. E. Hilgers and B. J. Calderwood of Hays, Kansas. The autopsy report as well as the entire heart, thoracic aorta and blocks of several organs

were received and examined at the University of Kansas Medical Center.

During the course of the patient's hospitalization his two sisters who were known to have heart murmurs were examined at this institution. These two women, aged twenty-three and thirty-three, were essentially asymptomatic. One had slight cardiac enlargement. Electrocardiographic examination revealed first degree heart block and right bundle branch block in both. It was believed that both have atrial septal defects. Neither has, as yet, been studied by cardiac catheterization. A marked left axis deviation in one suggests the probability of an ostium primum defect.*

AUTOPSY FINDINGS

The body was that of a thin white male appearing approximately nineteen years of age. The skin was moderately cyanotic throughout. There was an incision at the fifth intercostal space which was the result of thoracotomy for cardiac massage after death had occurred. The usual Y-incision was made and there was found a tremendously enlarged heart with a remarkably hypertrophied left ventricular myocardium. It was noted that the aorta was extremely small throughout its course. The heart was removed with the aorta intact down to the diaphragmatic entry. The lungs were wet and filled with edema fluid throughout. The left lung was small, the greater portion of the left pleural cavity being occupied by the heart. The abdominal contents were essentially normal except that the liver was relatively small and the cut surface presented a nutmeg appearance. The kidneys were of normal size and appeared to be somewhat pale and fibrotic.

The heart was fixed in formalin when received in this laboratory. It was tremendously enlarged, weighing 1,300 gm. The enlargement was generalized but most conspicuous in the left ventricle. The pericardium was smooth and glistening. The subepicardial fat was thin. The coronary arteries were pliable, thin and patent. On transection the myocardium was firm and pale gray. Within the wall of the left ventricle and interventricular septum were seen extensive grayish white areas. The atria were enlarged and the atrial wall measured about 0.3 cm. on thickness. Their endocardium was not thickened. The wall of the right ventricle measured 1.7 cm.; the left 3.7 cm. (Fig. 2). The interventricular septum measured 3.5 cm. in thickness. The trabeculae carnae and papillary muscles were hypertrophied. Several blood clots were present on the endocardial surface of the left ventricle. The approximate circumference of the valves were as follows: tricuspid 12.5 cm., pulmonic 8.0 cm., mitral 11.0 cm. and aortic 5.0 cm. The valves revealed no deformities. The leaflets were soft and pliable with no vegetations. The pulmonary artery had a circumference of 6.4 cm. The circumference of the aorta measured 5.0 cm. at its origin and 3.1 cm. in the mid-thoracic region (Fig. 3). The great vessels had normal origin and drainage. The coronary arteries arose from normal sinuses of Valsalva and pursued a normal course. Section revealed the absence of atheromatous change. In relation to the enlarged heart the coronary vessels appeared small. The foramen ovale was closed. No septal defect was present. The ductus arteriosus had been obliterated. The bundle of His and its branches were identified.

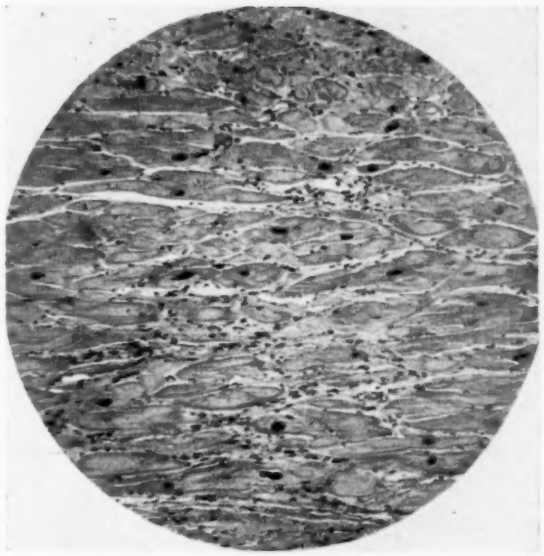

FIG. 4. Microscopic section of the left ventricular myocardium showing hypertrophied muscle fibers with large vesicular nuclei, areas of degenerating muscle fibers and increased interstitial connective tissue. Some muscle fibers show areas of hyalinization.

*Microscopic Findings:* Sections of the left ventricle (Fig. 4) and interventricular septum showed areas of degenerating muscle fibers. The fibers were hypertrophied with large vesicular nuclei of various sizes. Certain portions of the muscle fibers showed "hyalinized areas" where myofibrils and striations disappeared. Some muscle fibers had lost their cellular outline with replacement by fibrous connective tissue in many areas. Fibroblasts were seen in the stroma with few chronic inflammatory cells and capillaries. Few vacuoles were seen in the muscle fibers. Special stains for glycogen and amyloid (PAS with diastase, Congo red, crystal violet and toluidine blue) failed to show the presence of these substances. A few PAS-positive nuclear inclusion bodies were seen. The right ventricle and atria also revealed hypertrophy of muscle fibers with large vesicular nuclei. There was an increase in collagen connective tissue in the epimysium and endomysium. There seemed to be a scarcity of small blood vessels in the myocardium. The bundle of His was identified and revealed no discernible lesion.

* This sister has now been extensively studied and evidently has idiopathic myocardial hypertrophy.

FIG. 5. Photographic view of root of aorta from within left ventricle. Note the unusual plicating or overlapping of the aortic wall (arrow A) just distal to its origin. Finger tip (arrow B) within the lumen of the aorta, pointing down toward the cavity of the left ventricle, demonstrates how this overlapping diminishes the circumference of the aorta.

The epicardium and endocardium revealed some increase in fibrous tissue with increased vascularity. Several thrombi were attached to the endocardium of the left ventricle and organization had started to take place at the site of attachment. No atherosclerosis was noted in sections of a main coronary artery.

Sections of the lungs showed edema fluid in the alveoli with thickening of alveolar septa due to congestion by red cells. Many macrophages, some containing hemosiderin, were seen in the alveoli. The liver revealed congestion of the sinusoids by red cells, especially around the central veins, with degeneration of hepatic cells. The kidneys and spleen also showed congestive changes. Sections of the adrenals contained a moderate amount of lipoid in the cortical cells. The adrenal medulla was relatively prominent. The aorta revealed that the tunica intima was lined by endothelium. No subintimal lipoid deposition was noted. The tunica media was made up of both muscle and elastic tissue.

## COMMENTS

*Types of Idiopathic Cardiomegaly:* This case would seem to fit into that syndrome which has been described for a number of years by Levy and associates[11–13] as idiopathic cardiomegaly. It is an uncommon form of heart disease. Levy[13] described five cases among 3,154 autopsies performed in ten years at the Presbyterian Hospital in New York. Levy and Von Glahn[12] had previously reported ten cases. These fifteen cases are comprised primarily of young adults, especially young men, with similar clinical and pathologic findings. All had marked cardiomegaly in the absence of the usual causes of cardiac enlargement. Early in the clinical course the patients may be relatively asymptomatic in the presence of considerable cardiomegaly. The duration of life from the onset of symptoms to death varied from a few days to five years. Cardiac insufficiency was present in all and death occurred either suddenly or from gradual progressive cardiac failure. Various arrhythmias and conduction defects were common. These included atrial fibrillation, atrial flutter, paroxysmal atrial tachycardia, ventricular tachycardia, nodal tachycardia, partial and complete atrioventricular block and bundle branch block. Peripheral embolization was frequently observed. Pathologically there was cardiac hypertrophy, often to an extreme degree. Mural thrombi were common. Every case showed hypertrophy of individual muscle fibers with a varying degree of fragmentation, necrosis and vacuolization of these fibers. Myocardial fibrosis varied from none to extensive. Occasional areas of endocardial thickening were found, usually beneath thrombi. There were foci of lymphocytes beneath thrombi and endocardium. Rare groups of chronic inflammatory cells were present around small vessels and nerves.

A familial form of idiopathic cardiomegaly has been described[6,7,14] for which William Evans[6] has proposed the name "familial cardiomegaly." These cases had a clinical course and pathologic findings almost identical to the nonfamilial form. The usual causes of cardiomegaly were absent. Symptoms were often absent or mild for some time in the presence of conspicuous cardiomegaly. Stokes-Adams attacks, arrhythmias and conduction defects were common as were sudden death or death following syncope or paroxysmal tachycardia. At necropsy cardiac hypertrophy was often extreme. The heart in one of Evans' patients weighed 1,134 gm. There was a variable degree of fibrosis of the

myocardium with hypertrophy of remaining muscle fibers. Some patients have had excessive glycogen deposits in the myocardial fibers.[6,14] These cases, then, are quite similar to the non-familial form of idiopathic cardiomegaly. Indeed, Evans,[6] in his original discussion of familial cardiomegaly, describes several other suggestive cases in which other members of the family were not affected. Byron Evans[15] described four patients with cardiomegaly of obscure etiology in whom necropsy revealed myocardial fibrosis of variable degree. Two had hypertrophy of the myocardial fibers, two had endocardial fibrosis and three had mural thrombi. One had a smaller than normal aorta. None had similarly affected relatives but he believed that three of these patients were examples of "familial cardiomegaly." The fourth patient had diffuse infiltration of the interstitial connective tissue with chronic inflammatory cells and was thought to have active myocarditis.

Other cases of idiopathic cardiac enlargement have been described in which marked thickening of the endocardium and subendocardial fibroelastic tissue accompanied the myocardial fibrosis without hypertrophy of myocardial fibers.[16,17] No convincing explanation has yet been offered to explain these various forms of idiopathic cardiomegaly. That they are not congenital is attested to by the fact that occasional patients have had normal-sized hearts demonstrated by x-ray examination several years prior to death.[13] Myocardial fibrosis is known to occur following myocarditis or myocardial infarction. It may also occur secondary to myocardial hypertrophy and dilatation due to any cause.[18]

*Hypoplasia of the Aorta:* Another finding of interest in the case reported herein was the hypoplastic aorta (Figs. 3 and 5). Luisada gives 20 mm. as the average diameter of the thoracic aorta.[18] Ikeda,[19] after a survey of several series of necropsy measurements, determined the average circumference of the mid-thoracic aorta to be 4.4 cm. Werley[20] relates that Aschoff found 3.83 cm. in circumference to be the smallest thoracic aorta found in autopsies on 176 World War I soldiers. According to these observations the aorta in this case falls within the hypoplastic range, but the significance of this finding is uncertain. A number of cases and series of cases have been reported in which young adults have died either suddenly or following progressive congestive heart failure and at autopsy hypoplasia of the aorta was the only finding to explain their heart disease.[19–23] Some of these same authors,[19,22] however, have also observed that hypoplasia of the aorta is not uncommonly found at autopsy in the absence of cardiac disease. In 4,500 autopsies at the University of Texas, Werley, Waite and Kelsey[22] found twenty-five instances of aortic hypoplasia, among which there were only four cases of cardiac enlargement.

Hypoplasia of the aorta has been observed to occur secondary to, or at least in association with, other forms of cardiovascular disease.[24–28] It can occur congenitally in association with other congenital cardiovascular anomalies.[24] It may also be developmental, secondary to a low cardiac output caused by other cardiovascular disease.[18] Some cases of cardiac hypertrophy ascribed to hypoplasia of the aorta had pathologic findings in the heart similar to those described in idiopathic cardiomegaly.[20,22,28] Some of these cases may actually represent further examples of idiopathic cardiomegaly with secondary aortic hypoplasia. It is not, however, possible to invoke this explanation in all cases of heart disease attributed to hypoplasia of the aorta since many of these patients had normal microscopic findings in the heart, and from their histories would not have seemed to be in cardiac failure during their developmental years. Whatever the case may be, the presence of aortic hypoplasia in apparently unaffected individuals, together with its occurrence secondary to other forms of heart disease, makes it difficult to determine its significance as a primary cause of heart disease. The history suggesting cardiac insufficiency during the developmental years and the microscopically normal aortic wall lead us to believe that the patient reported on herein had idiopathic cardiomegaly with secondary aortic hypoplasia.

## Summary

A case of extreme idiopathic cardiomegaly associated with a hypoplastic aorta is reported. The heart weighed 1,300 gm. The patient's clinical course was characterized by recurrent and protracted Stokes-Adams syndrome which terminated in sudden death.

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# Cor Triloculare Biatrium with Pulmonary Stenosis*

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COR TRILOCULARE BIATRIUM is a rare form of heart disease which is the result of the failure of the ventricular septum to develop normally. It is characterized by both mitral and tricuspid orifices opening into a single ventricle. Holmes[1] described a case of this anomaly in 1823. Since then many authors have described their cases in the literature. Abbott[2] described thirteen cases in her series of 1,000 cases of congenital heart disease; Clawson[3] noted seven in his series of 141 and Rogers and Edwards[4] nine cases with the clinical and pathologic features. Campbell et al.[5] in 1953 reviewed seventy-eight cases from the literature and added six of their own. However, in twenty cases the interatrial septum was completely absent, and these represented the bilocular heart rather than cor triloculare biatrium. Van Buchem and coworkers[6] in 1957 described a patient with cardiac catheterization and angiographic findings and estimated that approximately sixty cases were listed in the literature.

## CASE REPORT

A twenty-nine year old white woman, 5 feet, 9 inches in height and weighing 116 pounds, was admitted to the Bailey Thoracic Clinic with the chief complaint of shortness of breath and fatigue. She was born with a heart murmur. Cyanosis was first noted when she was five years of age, and this was intermittent in type, noted especially during exertion or excitement. Some clubbing of the fingers was noted about the same time. Her activities, however, were not restricted during the growing years and physical and intellectual development had been normal. No history of squatting was obtained. She has had exertional dyspnea, some fatigue and vertigo. She gave a recent history of slight and occasional ankle swelling. Fainting spells had occurred about four times in the past year, the most recent one occurring about one month before admission. The patient was studied in 1957 for evidence of kidney disease and a poorly functioning left kidney was found.

*Physical Examination:* This revealed obvious cyanosis of the fingers and lips as well as toes. The veins of the neck were slightly distended but did not pulsate. Examination of the heart revealed a rough systolic murmur over the aortic and pulmonic areas. A grade 4 harsh systolic murmur was heard best in the second, third and fourth interspaces to the left of the sternum. The pulmonic second sound was accentuated. The blood pressure was 118/66 mm. Hg and the pulse was 92/min.

*Laboratory Findings:* Hemoglobin was 20.4 gm. per cent, and hematocrit 71 per cent. The urine examination showed a specific gravity of 1.009; tests for sugar, protein and acetone gave negative results. Occasional hilar casts and white blood cells were noted. The blood urea nitrogen was 8 mg. per cent. The Fishberg concentration test showed urine specific gravity to be fixed between 1.008 and 1.011. The phenosulfonphthalein test revealed 64 per cent excretion of the dye at the end of two hours. Serum creatinine was 1.6 mg. per cent.

The electrocardiogram (Fig. 1) showed right axis deviation, extreme clockwise rotation of the heart and right ventricular hypertrophy. The teleroentgenograms (Fig. 2) showed no evidence of cardiac enlargement. The lung fields were normal except for slight thickening of the apical pleura on the left side.

*Catheterization Findings:* Cardiac catheterization was performed on March 6, 1958. The following data were obtained:

| Chamber | Oxygen Content (vol. %) | Pressure (mm. Hg) |
|---|---|---|
| Superior vena cava | 14.9 | ... |
| Inferior vena cava | 16.2 | ... |
| Right atrium | 15.3 | 3 |
| Right ventricle | 21 | 110/4 |
| Brachial artery | 21.1 | 110/68 (76) |

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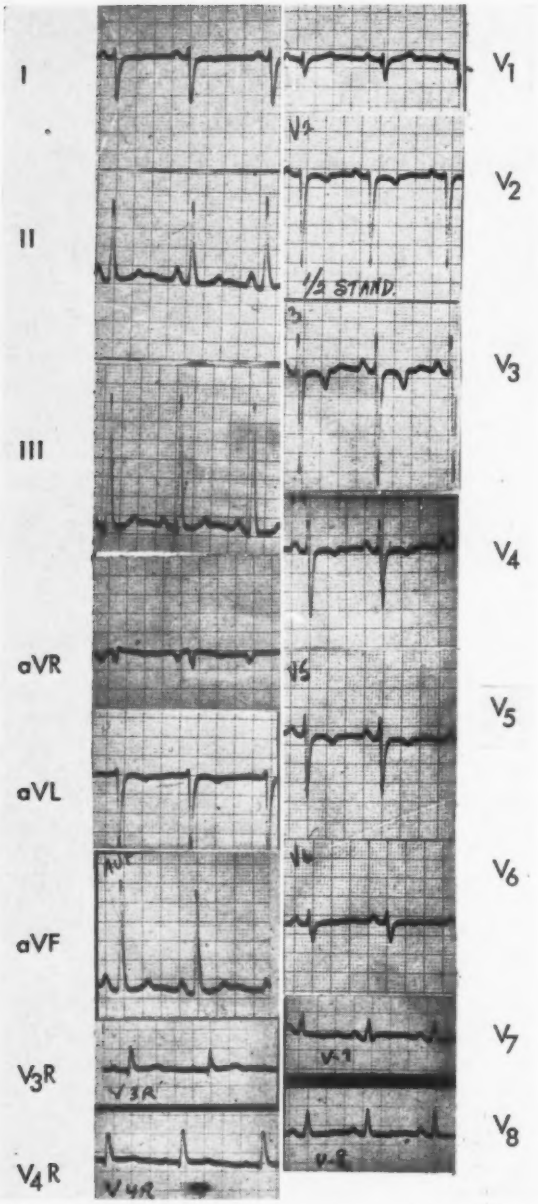



FIG. 1. Standard leads show right axis deviation. Additional leads (at bottom) show confirmatory evidence of right ventricular hypertrophy.

The oxygen capacity of the blood was 29.0 vol. per cent and the peripheral saturation 73 per cent (92 per cent is regarded as normal in this laboratory). The catheter passed from the right ventricle into the aorta. The pulmonary artery could not be entered on numerous attempts.

*Operative Findings:* A tentative diagnosis of tetralogy of Fallot was made and the patient was operated upon for the correction of the defect by open heart technic. The right ventricle appeared markedly dilated. On exploration of the heart through right ventriculotomy, pulmonary valvular stenosis was found.

The pulmonic stenosis was corrected by Brock's procedure. There was no ventricular septum present between the right and left ventricle. Repair of the common ventricular chamber was not feasible.

Following surgery the patient remained in profound shock and died eight hours postoperatively.

*Autopsy Findings:* The heart weighed 350 gm. The right atrium was dilated. The inferior and superior venae cavae were normal in position. The tricuspid valve measured 5 cm. in diameter. The left atrium was small in size and the pulmonary veins entered normally. The mitral valve measured 3 cm. in diameter. There was no evidence of an interventricular septum or rudiments of it (Fig. 3). The papillary muscles with their chordae tendineae of the tricuspid valve were implanted in the apex of the common ventricle.

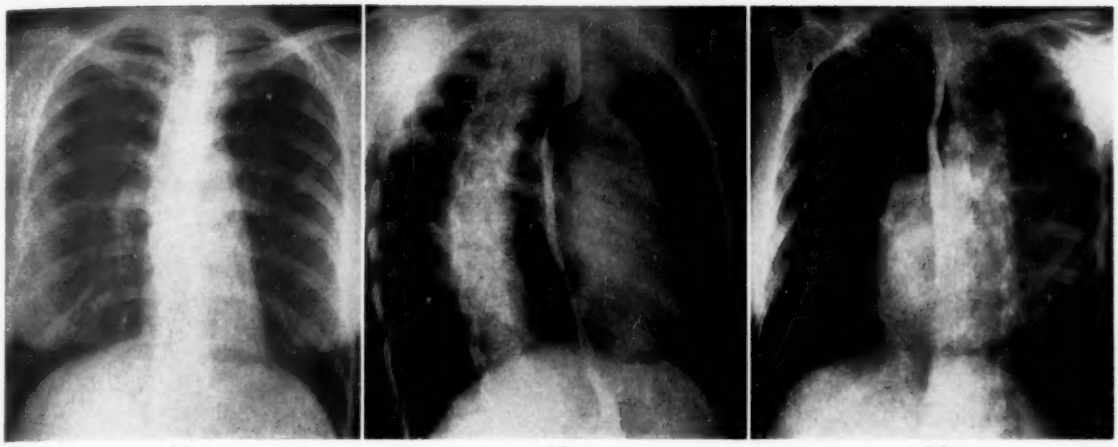
There was a transposition of the great vessels. The pulmonary artery was located posteriorly and the aorta anteriorly. The pulmonary orifice was stenotic and measured 1.5 cm. in diameter, and the pulmonary valve was bicuspid. The ductus arteriosus was closed. The myocardium of the common ventricle measured 1.5 cm. in thickness. The origin and the course of the coronary arteries were normal.

## COMMENTS

### EMBRYOLOGY AND PATHOLOGY

At an early stage of development the primitive heart, which has been a straight tube, becomes S-shaped with two bends in different planes. The ridge between the bulbus cordis and the common ventricle atrophies and the aortic septum develops. The aorta arises from the common ventricle posterior to the bulbus cordis while the anterior portion of it forms the outflow tract of the right ventricle from which the pulmonary artery arises. In cor triloculare biatrium the development of the heart is arrested at this stage. The bulbus cordis persists as a rudimentary outlet chamber. Both great vessels may arise from the rudimentary chamber or one may arise from the common ventricle and the other from the rudimentary outlet chamber.

Brown[7] divides these cases into three types: (1) the great vessels are transposed so that the aorta arises from the rudimentary chamber and pulmonary artery from the main ventricle (the most common type); (2) the aorta and pulmonary artery arise from the rudimentary chamber (a less common type); and (3) a rare type occurs in which the aorta arises from the main ventricle and pulmonary artery from the rudimentary chamber. Taussig[8] and Heath[9] be-



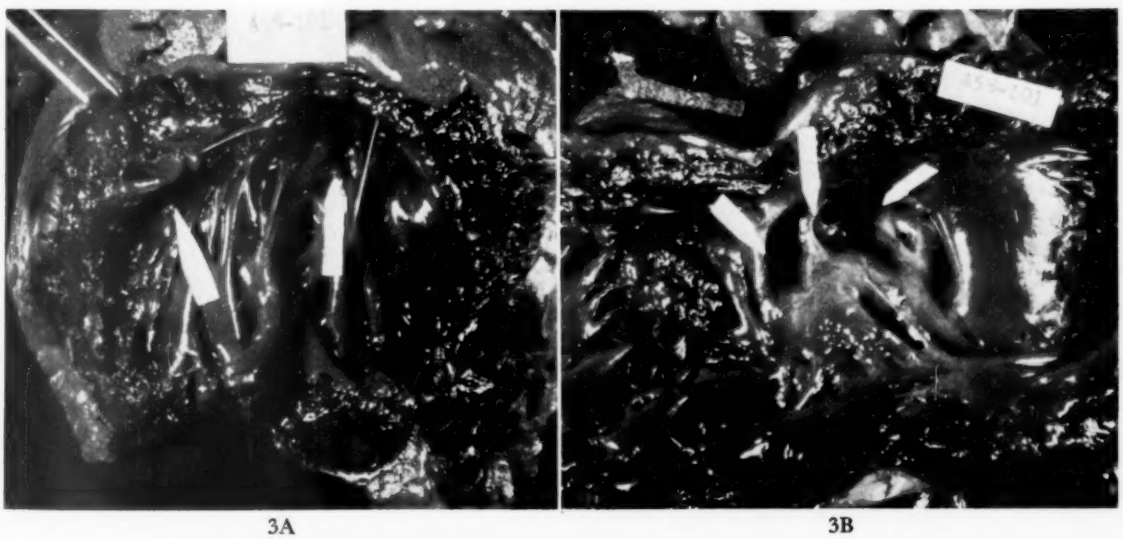
2A 2B 2C

FIG. 2. A, posteroanterior view of heart: normal. B, right anterior oblique view. C, left anterior oblique view.

lieve that this conception of the origin of the great vessels is important for when the pulmonary trunk arises from the rudimentary chamber it is small, but when it arises from the main chamber it is large and carries an adequate blood flow to the lung for aeration. The cyanosis in the latter group is less frequent and less pronounced than in the former. In the former group Taussig[8] estimates the average survival period to be only a few months while in the latter it is longer with an average period of six years.

INCIDENCE AND PROGNOSIS

As has been already mentioned, the transposition of the aorta and the pulmonary artery is present in the majority of cases. It was present in forty-eight of the eighty-five cases reviewed by Campbell.[5] The incidence of obstruction to pulmonary blood flow is less frequent. Again Campbell and co-authors state that pulmonary atresia was present in fifteen and pulmonary stenosis in twenty of the eighty-five cases. This has been mostly valvular. They believe that the presence of pulmonary stenosis has a favorable influence on prognosis. The average age of those with pulmonary stenosis is estimated to be seventeen years against six and one-half years of those without it. The positive effect of mild pulmonary stenosis can



3A 3B

FIG. 3. A, view of mitral and tricuspid valves emptying into common ventricle. B, pulmonary artery, cristus supraventricularis and aorta. Absence of intraventricular septum.

be easily understood if consideration is given to the hemodynamics in this condition.

The relative volume of blood flowing from a common ejective source into the two great arteries depends upon the magnitude of the resistance offered by the systemic and pulmonary vasculature. After birth the resistance to pulmonary blood flow is much less than the systemic blood flow. In a case of cor triloculare biatrium it is expected that a greater flow of blood would go to the lungs and less to the systemic circulation. The patient with this condition who lives through adulthood probably has a regulatory mechanism which determines the relative amount of systemic and pulmonary blood flow. This regulatory mechanism may be found in the tone of the pulmonary vasculature. Pulmonary hypertension would be part of such a regulatory mechanism.[10] The presence of pulmonary stenosis in itself prevents the flooding of the lung fields and its adverse effect on the pulmonary vasculature. However, pulmonary stenosis of a severe degree or pulmonary atresia would prevent adequate oxygenation of blood and accentuate cyanosis. No patients with pulmonary atresia lived beyond the age of one year.[5]

The prognosis in cor triloculare biatrium is variable and depends on the adaptive mechanisms coming into play. The over-all prognosis is bad and more than 50 per cent of the patients die before the age of one year. The longest surviving patient, aged fifty-six, was described by Mehta and Hewlett.[11] In the nine cases described by the Mayo group[4] six patients died before the age of one and the longest survived age was eight years. The patient described herein was twenty-nine years old. The presence of pulmonary stenosis appears to have had a beneficial effect on the prognosis in this patient.

### SYMPTOMS, PHYSICAL FINDINGS AND DIAGNOSTIC METHODS

Most patients born with this anomaly are severely symptomatic and more than 50 per cent die early in childhood. The majority of the patients are born with cyanosis or it develops early in life. Usually the degree of cyanosis is proportional to the severity of dyspnea and fatigue.

A systolic murmur in the left parasternal area is the most common auscultatory finding. The murmur is usually rough and loud. In the present case the murmur was loudest in the pulmonary area and was accompanied by a thrill. This particular physical finding in this case can be ascribed to the presence of pulmonary stenosis. The pulmonic second sound was of normal intensity although the pulmonary stenosis was of the valvular type.

Electrocardiography and radiology are of little help in distinguishing this condition from other cyanotic heart diseases, particularly tetralogy of Fallot. There is no common or easily recognizable electrocardiographic pattern for this condition.[8] Right axis deviation and right ventricular hypertrophy, as seen in this patient, are the most common findings.[5] The QRS complexes are of normal duration in the majority of the cases described even though the course of the bundle of His is totally abnormal because of the absence of the ventricular septum. In two of the cases reported by Edwards and Chamberlain[10] there was left axis deviation.

There are no particular radiographic patterns ascribed to this condition. Cardiac enlargement has been reported by Glendy and co-workers,[12] Edwards and Chamberlain[10] and Edwards and Rogers.[4] In our patient the heart was normal in size and there was no prominence of the pulmonary conus and hilar vessels.

Cardiac catheterization was of no particular help in this case as the catheter could not be maneuvered into the pulmonary artery. Pulmonary hypertension (125/70 mm. Hg) with identical pressure and oxygen saturation in the ventricle, pulmonary artery and the aorta has been reported in a case uncomplicated by pulmonary stenosis.[6]

### SUMMARY

A report of an adult patient with cyanosis is presented and the difficulties encountered in reaching the diagnosis are mentioned.

Most patients with cor triloculare biatrium are severely symptomatic and more than 50 per cent die early in childhood. Those who survive to adolescence or adulthood probably have adaptive mechanisms as have been outlined herein. Most of these patients are born with cyanosis or it develops early in life.

In those who are acyanotic or mildly cyanotic a large pulmonary artery arising from the main part of the common ventricle is present, allowing a great volume of blood to be oxygenated in the lungs. Usually the degree of cyanosis is directly proportional to the severity of dyspnea and fatigue. The beneficial effect of pulmonary stenosis in cor triloculare biatrium is also suggested.

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# Coarctation of the Aorta in Father and Son

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THE INCIDENCE of congenital cardiac defects is apparently more common in certain families than pure statistical chance would suggest. McKeon and his co-authors[1] state that a certain familial predisposition to congenital heart disease has been demonstrated. Campbell[2] has also found that the causes of congenital heart disease are chiefly genetic, based on the observation that these cardiac defects occur more frequently in siblings and relatives of affected individuals. Although coarctation of the aorta is a relatively common congenital cardiac anomaly of the non-cyanotic group, there have only been a few reports in the literature of verified cases occurring in the same family. Kjellberg et al.[3] found one case of coarctation of the aorta in which another member of the family also had the defect. Taylor and Pollock[4] reported coarctation of the aorta in three members of the same family, a mother and two children. Walker[5] reported coarctation in a father and son and there is another report in the Scandinavian literature by Klemola[6] of two brothers with this identical lesion. Lamy[7] found one case of sibship in fifty-four cases of coarctation. Yet, the exact genetic patterns in which congenital cardiac hereditary traits are determined has never been clarified graphically.

This report deals with two proved cases of coarctation of the aorta occurring in a father and his only son. The defect found in the son was treated surgically and corrected. The defect in the father, who was forty-eight years old at the time of the diagnosis, was apparent clinically, but the patient refused operative treatment. It is believed that these two cases present a good illustration of the presumptive hereditary features of this disease.

## CASE REPORTS

CASE 1. R. G. was a twenty-one year old white man who was first seen in my office in March 1958. He was essentially asymptomatic at the time of the examination, but reported for the examination following a medical discharge from the United States Navy after he had been found to have coarctation of the aorta. His past history was essentially normal except for some easy fatigability and questionable shortness of breath with moderate exertion. When he was nine years of age, he was told that he had a "heart murmur" and was advised to limit his activities. There was no history of rheumatic fever, paroxysmal nocturnal dyspnea, hemoptysis or edema.

*Physical examination* revealed an adult white man, moderately well developed and well nourished, weighing 147 pounds. Pulse was 88, temperature 98.6°F. and respirations 16. Blood pressure was 150/90 to 180/100 mm. Hg in the left arm and slightly higher in the right arm, but the differential was less than 15 mm. Hg systolic. There were weak femoral pulsations. Blood pressures in the lower extremities measured over the popliteal fossa were approximately 80/50 mm. Hg. Examination of the heart revealed a normal sinus rhythm and no apparent cardiac enlargement. There was a grade 1 systolic murmur, heard best in the second and third left interspaces. There was another systolic murmur, grade 1–2, heard over the right interscapular area.

*Laboratory data:* Red blood count was 4.75 million per cu. mm.; hemoglobin, 15 gm.; white blood count, 6,300 per cu. mm. with a normal differential; hematocrit, 46 per cent; sedimentation rate, 17 mm. per hour uncorrected; blood type "O," Rh positive; urinalysis was normal; blood urea nitrogen, 11 mg. per cent. An electrocardiogram taken at this time was within normal limits. An x-ray film of the chest revealed mild notching of some of the ribs with clear lung fields. The cardiac silhouette showed elongation of the aorta with increased pulsations, but no chamber enlargement.

*Surgical Findings and Course:* The patient underwent surgery on April 22, 1958. The description at the time of operation was as follows: "The proximal aorta and the left subclavian artery were enlarged, especially the latter artery, which was the size of the distal aorta. The distal aorta was of normal size. The intercostal arteries were tremendously dilated. The ligamentum arteriosum originated from the proximal aorta 0.5 cm. proximal to the coarctation. The ligamentum arteriosum had a small pinpoint lumen which extended partially from the aortic side toward the pulmonary artery. The segment of the coarctation was dissected and an end-to-end anastomosis was performed. After con-

clusion of surgery the patient had very good femoral and dorsalis pedis pulses."

The patient had a stormy convalescence because of leakage that occurred through the arteriosclerotic segments of the aorta, but healing eventually took place and the patient is in good condition at this time. Follow-up in the office after complete healing revealed the blood pressure in the arms to be approximately 132/82 mm. Hg and the pulsations of the lower limbs to be strong and vibrant.

CASE 2. N. G. was a forty-eight year old white man who was the father of R. G. He had been essentially asymptomatic throughout his life. His only contact with physicians had been with periodic employment "physicals" as well as an insurance examination made many years ago. He was brought to the office by his wife because of a hypertensive reading made during a routine examination prior to a contemplated blood donation.

The patient drinks excessive quantities of beer and has noted some swelling of the face upon arising in the morning especially after a weekend bout of drinking. There were no symptoms of renal disease, headache, pain in the legs, paresthesias or weakness. The patient was subjected to a herniorraphy in 1950, but at that time hypertension was not recorded.

*Physical examination* revealed a fairly well developed white man weighing 127 pounds. Pulse was 70, temperature 98.6°F. and respirations 18. The blood pressure in the left arm was 220/110 and in the right arm 170/90 mm. Hg. The blood pressure in the lower legs was approximately 120/70 mm. Hg and the femoral pulses were barely palpable. The heart was not enlarged and there was a normal sinus rhythm. There was a blowing systolic murmur, grade 2, heard along the left sternal border as well as over the chest area posteriorly. The murmur was less intense at the apex and in the aortic area and became louder over the lower left parasternal area and somewhat harsher in quality. There was no diastolic component noted. The abdominal examination revealed no abnormalities. Increased arterial collateral pulsations were palpable over the chest posteriorly.

Fluoroscopic examination showed some enlargement of the left ventricle. An x-ray film of the chest revealed rounding of the left cardiac border, some elongation and bulging of the aortic arch segments and marked notching of many of the ribs. The lung fields were clear. An electrocardiogram disclosed evidence of minor T wave changes indicative of early myocardial non-specific damage.

The patient was seen in consultation with the cardiac surgical staff who believed that surgery was indicated in spite of the patient's age, but he refused to agree to this form of therapy. The patient's general physique is similar to that of his son except for the fact that he is 1 or 2 inches shorter and about 15 pounds lighter.

## COMMENTS

Coarctation of the aorta presumably occurs due to imcomplete formation and fusion of the embryonic fourth and sixth aortic arch. The incidence of coarctation was noted to be 5.5 per cent in a series of 1,395 congenital cardiac cases studied by Gasul and Fell.[8] It was the fourth most common anomaly in the non-cyanotic group. Embryologic studies quoted by Taussig[9] indicate that cardiac malformations result from developmental error, either arrest or retardation of the growth or differentiation of some of the specific parts. Corner[10] states that the same malformation may result from a "bad egg in a good environment as from a good egg in a bad environment." Other malformations frequently found along with coarctation of the aorta are bicuspid aortic valves, patent ductus arteriosus and atrial septal defects. There are also other congenital defects which occur with coarctation such as hypospadias or absent left kidney.

The hereditary aspects of this report are most interesting and stimulating. The father was of a unique family, having six brothers, all alive and well, ranging from fifty-two to sixty-seven years of age. There were no daughters in the family. The grandfather died at the age of eighty years with diabetes. The grandmother died at the age of eighty years. N. G.'s brothers work in a progressive industrial establishment which performs careful, thorough, yearly physical examination on all its employees. All the brothers were industrious careful workers and remained with this particular concern all their productive employable lives. In reviewing their histories and physical and x-ray findings with the medical department of this industrial concern, it was found that only two had evidence of hypertension. All the brothers were reexamined and found to be in excellent physical condition. The two who had mild hypertension had a labile blood pressure and revealed no stigmas of coarctation of the aorta. The genetic features of coarctation, therefore, are apparently of a recessive nature since the element of chance and appearance of the defect would be most improbable in seven brothers if there were any dominant features to the chromosomal pattern. There were no other siblings of R. G. with which to verify further genetic studies. It is possible that a lethal factor in the genetic make-up acted as a natural filter. As for the general physical make-up of father and son, they were quite similar in appearance, body build and musculature.

A defect of the genes appears to be of importance in the production of many malformations according to Taussig.[9] In certain instances a strong hereditary tendency is apparent and the cases reviewed in this article lend support to this thesis. Another supporting feature is the finding that defects of the aorta, particularly coarctation, are more frequent in men and this study follows the pattern.[7] But the hereditary pattern does not approach the hypothesis of a single penetrant gene. Yet, no judgment can be made in regard to genetic factors in coarctation because of the paucity of data. These two cases may lend some support to a strong genetic theory.

## Summary

This report deals with two verified cases of coarctation of the aorta, one occurring in a father and the other in his son. It is believed that the genetic factors played an important role in this particular study. Although coarctation of the aorta is noted not infrequently, it has not been reported too often as occurring in the same family.

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# Rupture and Dissection of Aorta in Marfan's Syndrome*

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MARFAN'S SYNDROME is a rare familial condition characterized by a congenital defect in development of mesenchymal tissue. It is manifest clinically in the skeletal, ocular and cardiovascular systems. The outstanding anomalies are: (1) *Skeletal:* Arachnodactyly, dolichocephaly, cavum pectinatum or excavatum, high arched palate, kyphosis and scoliosis and long extremities; (2) *Ocular:* Congenital dislocation of the lens, tremulous iris; (3) *Cardiovascular:* Congenital heart disease and media necrosis cystica of the aorta.

Clinical features include sparsity of subcutaneous fat and weakness of the joint capsules leading to a marked hypermobility of the joints as evidenced by genu valgus, pes planus and dislocation of the hips. Recently, McKusick[2,3] reviewed the literature and discussed the syndrome in its entirety. The following report is that of a patient who presented a clinical picture referable to the cardiovascular abnormality. This will be the twenty-third published case[6–25] of this syndrome associated with rupture and dissection of the aorta. Of interest, also, is the fact that the diagnosis was made antemortem on the basis of clinical findings.

## CASE REPORT

Mrs. J. V., a twenty-four year old nulliparous Puerto Rican sewing machine operator, was admitted by ambulance to the emergency room of St. Vincent's Hospital on November 30, 1955, complaining of severe interscapular pain. At 3 P.M. that afternoon, while sitting at work, she had suddenly felt an excruciating pain in the upper mid-back. The patient stated that the pain was steady but it radiated once, briefly, to both axillas. There was no diaphoresis or syncope. However, there were two episodes of emesis.

Past history revealed that before immigrating to the United States in 1952, she had never been seriously ill and had never sought medical or hospital care. However, five days after arriving here by plane, she was admitted to a New York hospital with the complaint of pain in the right side of the chest which developed during flight. Work-up and operation revealed a herniation of the colon and stomach through the foramen of Morgagni into the right side of the chest. At that time, the patient was normotensive and no cardiovascular abnormality was noted. She was asymptomatic when discharged ten days later.

Although the patient denied orthopnea, exertional dyspnea and edema, she did admit visiting a doctor for palpitation two weeks prior to this admission to St. Vincent's Hospital. She was told that she might have heart trouble and was given medication which relieved her symptoms. Family history revealed that a mother, father and eleven siblings were alive and well in Puerto Rico. Neither she nor her husband were aware of any clinical features of Marfan's syndrome in the family.

*Physical Examination:* The patient was a well nourished twenty-four year old woman, sitting up in bed, writhing with pain and complaining bitterly. She was not in shock or diaphoretic. Blood pressure was 170/70 mm. Hg in the right arm, 170/75 in the left arm and 150/60 in the left leg. Pulse was 60, respirations 20, temperature 98.6°F. The forehead was prominent with left frontal predominance. The eyes were normal. There was a high arched palate and wide separation and displacement of teeth. The thorax was long and narrow. There was a marked kyphoscoliosis of the lumbar spine and first degree cavum excavatum. The lungs showed normal pulmonary resonance and were clear to auscultation.

The heart was not enlarged to percussion. There was a loud diastolic murmur over the entire precordium associated with a diastolic thrill. This murmur was loudest at the fourth intercostal space at the left sternal border. A systolic murmur was also heard over the base of the heart and was transmitted into the carotid vessels. The arterial pulses were strong and equal bilaterally in the upper and lower extremities. The patient had arachnodactyly (Fig. 1) and a marked hypermobility of the joints

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FIG. 1. Hands: Arachnodactyly.

of the fingers, elbows and knees. Genu valgus and pes planus were evident (Fig. 2).

Because of the cardiac auscultatory findings, the character of the pain and the evident features of Marfan's syndrome, a diagnosis of dissecting aneurysm secondary to media necrosis cystica was made.

The x-ray film of the chest (Fig. 3) showed moderate left ventricular enlargement and dilatation of the arch and descending aorta. The electrocardiogram revealed a sinus rhythm and a horizontal axis. Urinalysis was normal. Complete blood count revealed a hemoglobin of 10.7 gm., white blood count 14,200 per cu. mm. with a shift to the left.

*Clinical Course:* The patient was first given Demerol®, and later morphine. In spite of analgesia, the pain was paroxysmal. Vital signs, with blood pressure being taken in both arms, remained steady. The lungs remained clear. At 12:40 A.M., approximately ten hours after onset of the illness, the patient uttered an agonizing scream and died a moment later.

## NECROPSY

*Chest:* On opening the chest cavity, it was noted that the mediastinum was shifted to the left and that

FIG. 2. Legs: Genu valgus and hypermobility of joints.

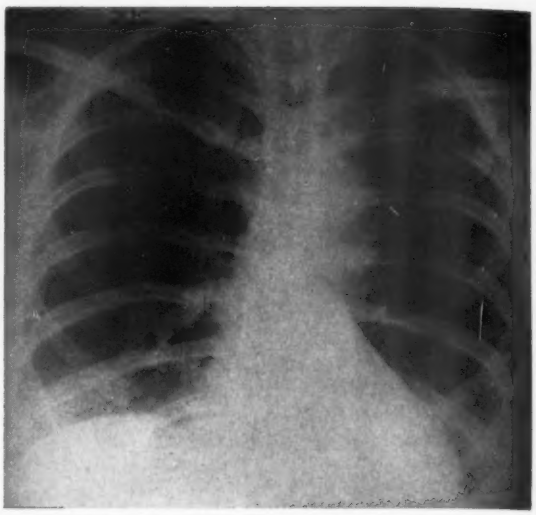

FIG. 3. X-ray of the chest on admission: moderate left ventricular enlargement, increased size of transverse and descending portions of aorta.

the right lung extended to the midline. The right pleural cavity contained 1,000 cc. of fluid blood and 700 gm. of blood clot. The posterior mediastinum, esophagus and posterior aspect of the pericardium were infiltrated with blood, extravasated from the thoracic aorta. Hemorrhage was also found behind the parietal pleura extending from the vertebral column laterally for some distance, and also in the substance of the diaphragm.

The thoracic spine was normal while the lumbar spine showed marked left scoliosis and lordosis.

*Heart:* The heart showed mild hypertrophy, weighing 390 gm. The pertinent pathologic condition was found in the aorta 1 cm. above the aortic cusps, where a transverse tear was observed through

FIG. 4. Aorta: Showing extent of rupture and dissection of its wall. Note blood clot within the dissected wall. Note coarctation (B), and ductus arteriosus (C).

the intima involving all but 1.8 cm. of the circumference of the vessel (Fig. 4). The tear extended through the intima into a sac within the media of the aorta. This sac, a typical dissecting aneurysm, extended from the aortic ring to the level of the renal arteries. Blood clot was found within the dissected wall. The intima of the aorta was smooth throughout. At the coarctation the lumen narrowed to 3.14 cm. in circumference. Above and below this the circumference of the aorta was 5 cm. and 5.5 cm., respectively.

The ductus arteriosus was patent throughout its length of 1 cm. and measured 0.3 cm. in diameter. Four centimeters beyond the ductus arteriosus, in the thoracic aorta, there was found a longitudinal tear through the adventitia, 1.5 cm. long, communicating with the posterior mediastinum.

*Microscopic Observations:* The entire aorta as far as the mid-thoracic area was cut into serial blocks. Sections from these were stained with hematoxylin and eosin and Weigert's elastic tissue stain (Fig. 5).

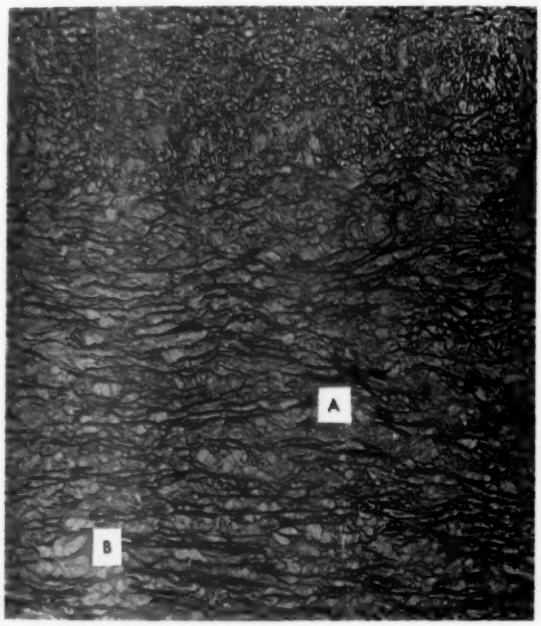


FIG. 5. Photomicrograph, low power: elastic tissue stain. Marked fragmentation of connective tissue and lamellae (A) and formation of small irregular mucus-filled cysts (B).

Throughout the media, from the aortic ring to beyond the arch, were numerous areas in which the elastic laminas were fragmented and disrupted. In some areas, irregular cavities filled with homogenous lightly staining, basophilic material were found. In other areas were found foci within the media, in which the smooth muscle cells were seen irregularly arranged and dispersed.

*Anatomic Diagnosis:* (1) Spontaneous rupture and dissection of the aorta, secondary to media necrosis aorta cystica, with hemorrhage into superior mediastinum, and the right pleural cavity; (2) Coarctation of the aorta; (3) Patent ductus arteriosus.

## COMMENTS

Despite rather abundant recent literature on Marfan's syndrome, there is a sparsity of necropsy material. Altogether there are approximately forty-five postmortem studies and of these nineteen have revealed rupture and dissection of the aorta. Despite this proportionately high number of dissections, the leading cause of death in this syndrome is congestive heart failure, secondary profound aortic regurgitation. The relationship between cardiovascular anomalies and Marfan's syndrome was first pointed out in the American literature by Piper and Irvine-Jones.[4] These authors reported one case and reviewed eighteen, eight of which probably had congenital heart disease. Baer, Taussig and Oppenheimer,[5] in 1943, were the first to note the presence of media necrosis cystica of the aorta in this condition, and in the same year, Etter and Glover[6] reported the first case of rupture and dissection. However, in 1918, in their report on aneurysms in childhood, Bronson and Sutherland[21] included a case of a seven year old boy who, in all probability, had Marfan's syndrome, although they did not recognize it as such.

In 1953, in an excellent paper, Goyette and Palmer[7] reviewed the records of the thirty-four autopsy cases up to that time and found the following: twenty-two patients had aortic lesions, twelve of which ruptured and dissected. Twenty-one also had valvular lesions and nine had septal defects. Only one had a normal heart. There are now ten more cases of dissection which were not included in their report.[8,11,12,18,20,22–25] In all of these, the lesion in the aorta was consistent with the media necrosis cystica as described by Erdheim[26] and Rottino,[27] that is, deficiency of the elastic and muscular fibers in the media and replacement by loose collagenous tissue. It is this change in the media which leads to rupture and dissection.

A diagnosis of dissecting aneurysm from clinical findings, in a young person, is a hazardous one. However, in this case, it was made with some finality because of the presence of the features of Marfan's syndrome. It is indeed likely that many young people who die from dissecting aneurysm have Marfan's syndrome

"forme fruste." This is graphically illustrated by Whittaker and Sheehan[8] who found dissecting aneurysms in a father and son, forty-six and twenty-two years old, respectively, neither of whom manifested mesodermal defects. However, in tracing the family, many overt forms of Marfan's syndrome were found also. McKusick[2] has found several probable cases in reviewing the records of dissecting aneurysms of the young in medical examiners' files. Levine et al.[28] reported a case of chronic dissecting aneurysm in a twenty-two year old person with arachnodactyly who was treated for rheumatic heart disease, scalenus anticus syndrome and as a neurotic. Although not recognized, their description makes this case one of probable Marfan's syndrome.

It is well to remember the importance of looking for features of Marfan's syndrome in young people with congenital heart conditions and acute thoracic episodes.

## Summary

A case of Marfan's syndrome is presented with autopsy confirmation of rupture and dissection of the thoracic aorta and presence of coarctation of the aorta and patent ductus arteriosus.

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# Coarctation of the Abdominal Aorta*

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THE PURPOSE of this report is to call attention to a form of coarctation which involves the abdominal aorta and also to stress the danger of abdominal aortography. The diagnosis of the typical case of coarctation of the aorta is easily made. However, when other than the thoracic aorta is involved, the diagnosis can be missed and may lead to an unnecessary major surgical procedure. If one is aware that the abdominal aorta is occasionally involved in this process, the diagnosis is readily made. In the usual case of coarctation, the area involved is immediately proximal or distal to the ductus arteriosus or ligamentum arteriosum. In rare instances, the descending thoracic aorta is involved. However, if such a lesion presents itself, it can be handled by thoracotomy.

A review of the literature reveals that nineteen cases of coarctation of the abdominal aorta have been reported. It is quite evident that there are many additional cases which have not been reported. Wood[1] has estimated that in approximately 2 per cent of the cases coarctation of the aorta occurs below the diaphragm. This lesion is often congenital in nature. However, in some instances, it is difficult to determine whether or not the narrowed area of the aorta may have resulted from an inflammatory reaction such as arteritis or periarteritis.

Of the nineteen reported cases, only eight patients were treated surgically. The remaining patients were either misdiagnosed and treated for ordinary hypertension or diagnosed at autopsy. Improvement did not occur in those treated by sympathectomy or nephrectomy. In three patients it was possible to perform a successful bypass. In one patient,[2] the spleen was removed and the splenic artery used to bypass the coarcted area. In the other two,[3,4] it was possible to produce a successful bypass by the use of the homograft. The following case report reveals an error in diagnosis which resulted in an unnecessary thoracotomy; it also indicates the dangers of abdominal aortography.

## CASE REPORT

A ten and a half year old boy was admitted to the Children's Hospital on August 21, 1954. He died on September 12, 1954. During a physical examination following an accident, he was found to have hypertension and was referred for a complete cardiovascular study. His past history was essentially noncontributory. He had always been well and had had no serious illnesses. He had noted some palpitation of the heart and flushing of the face on exertion. His parents had noted that his lower extremities were usually cold.

*Physical Examination:* The patient appeared to be well developed but rather obese. He was mentally alert. There was no cyanosis or clubbing of the fingers. His face was flushed. The pupils reacted normally. The eye-grounds were within normal limits. The lungs were clear.

Examination of the heart revealed no thrill or enlargement. The heart sounds were regular and of good quality. A short, rather harsh, systolic murmur was heard at the apex, along the left sternal border, and over the aortic area. The second aortic sound was louder than the second pulmonic sound. Blood pressure in the right arm was 205/130 mm. Hg; left arm, 200/130 mm. Hg. Blood pressure was unobtainable in either lower extremity.

A careful search revealed no enlarged collateral vessels over the posterior chest or around the shoulder girdles. The typical vascular type of murmur, which is commonly heard in the posterior chest in the ordinary case of coarctation of the aorta, was not present. However, such a murmur was heard in the lower posterior chest over the lower two or three ribs. During the preoperative physical examination in the hospital, it was noted that a grade 2 murmur was present at the xyphoid angle, which could be heard through to the posterior chest. The lower portion of the abdomen and the lower extremities were somewhat cooler than the upper half of the body. Feeble pulsations were present in both femorals.

* From the Children's Hospital, Los Angeles, California.

*Laboratory Findings:* Routine laboratory studies of the blood, including blood urea nitrogen, and urine were all within normal limits. The electrocardiogram was also normal. X-ray films of the chest (Fig. 1) revealed the size of the heart to be within the upper limits of normal. There was slight evidence of

FIG. 1. Roentgenogram of chest.

relative left ventricular enlargement. There was no evidence of an enlarged left subclavian artery. The aortic knob also appeared normal. No notching of the upper ribs was noted. There was minimal notching of the lower two or three ribs.

*Clinical Course:* In spite of the fact that two or three different examiners noted the rather loud murmur in the upper part of the abdomen and through the lower posterior chest, and although there was no definite evidence of the typical findings of coarctation of the aorta on the chest films, it was thought that this boy had coarctation of the thoracic aorta, and he was referred for surgical treatment.

On August 23, 1954, thoracotomy was performed but no evidence of coarctation of the aorta was noted. However, the surgeon did point out that the aorta narrowed as it passed through the diaphragm. The patient recovered from the thoracotomy rapidly. It was quite evident that we were dealing with coarctation of the abdominal aorta, therefore it was thought necessary to perform abdominal aortography in order to delineate the area of coarctation.

On September 1, 1954, by way of a catheter through the right femoral artery into the abdominal aorta, 25 cc. of 70 per cent Urokon® was injected. Twelve hours later the patient began complaining of headache and pain in his chest and abdomen. The white blood count rose to 37,000 per cu. mm. The urine revealed 4-plus albuminuria as well as red cells and casts. On September 4, the non-protein nitrogen rose to 146 mg. per cent. It was suspected that thrombosis of one or both renal arteries had developed. Despite all types of treatment, the patient's condition went downhill rapidly and he died in uremia on September 12, 1954.

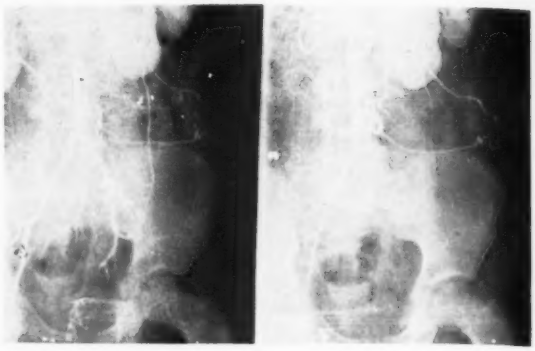

FIG. 2. Abdominal aortogram.

## AORTOGRAPHY

The abdominal aortogram (Fig. 2) was reported as follows: "The contrast substance was injected through a catheter in the abdominal aorta. The tip of the catheter is at the level of the renal arteries. Films demonstrate stenoses of both main renal arteries at their junction with the aorta. This narrowing only involves a segment 2 to 3 mm. in length. Narrowing of the aorta occurs just distal to the origin of the superior mesenteric artery. The inferior mesenteric artery apparently originates just distal to the narrowing of the aorta, because there is a rather extensive collateral circulation entering into the inferior mesenteric artery. Dilated intercostal vessels are noted. Beyond the coarctation, the aorta again assumes fairly normal caliber and branches into normal appearing iliac arteries. An aberrant renal artery arises from the aorta distal to the coarctation and supplies the lower pole of the right kidney.

*Conclusions:* "(1) Narrowing or coarctation of the aorta, involving a segment 5 to 10 mm. in length or less, located immediately distal to the origin of the superior mesenteric artery. (2) The left renal artery and upper right renal artery appear to be stenotic at their origins from the aorta. The narrowed segment again is very short in length. (3) The aorta beyond the superior mesenteric artery appears to be supplied mainly by the collateral circulation. (4) The blood supply to the right kidney is considerably less than the blood supply to the left kidney, and the lower pole of the right kidney is supplied from the low pressure side of the aorta. (5) The aortic coarctation is distal to the left renal artery and the upper right renal artery."

## AUTOPSY

The significant findings at autopsy involved the circulatory and urinary systems. There were no other congenital defects.

*Circulatory System:* "The heart weighs 260 gm. (normal weight 119 gm.). The great vessels appear to be enlarged and the branches of the thoracic aorta all appear larger than usual. The internal

mammary arteries are enlarged. The superior and inferior venae cavae enter the right auricle. The right auricular endocardium is smooth. The tricuspid valve is 7.5 cm. in circumference; the leaflets are smooth and delicate. The right auricle is 0.5 cm. in thickness. The pulmonary valve measures 4.0 cm.; the leaflets are three in number and delicate. The pulmonary artery is a thin-walled structure with a smooth yellow intimal surface. It divides into two pulmonary branches. The pulmonary veins enter the left auricle in the usual manner. The left auricular endocardium has a smooth surface. The mitral valve measures 7.0 cm.; the leaflets are thin and delicate. The left ventricle is thickened measuring 1.7 cm. The myocardium of the ventricles reveals no focal changes. The aortic valve measures 3.5 cm. There are three valve leaflets which are delicate. There are two coronary ostia about 2 mm. in diameter which are patent. Small atheromata are present above the aortic valve and just below the valve in the outflow tract. The endocardium in the outflow tract appears slightly thickened. A supernumerary vertebral artery emerges from the arch of the aorta. The aorta has numerous sclerotic areas on the intimal surface particularly around the ostia of the arteries branching off from it. Many of these arteries have almost a thin flap-like membrane over the orifice.

"In the abdominal aorta at the level of the celiac axis the aorta narrows down and is narrow all the way to the bifurcation. The diameter of the aorta at the level of the celiac axis is 2.5 cm. This is above the constriction. At the level of the renal artery it is 0.7 cm. Just slightly above the bifurcation of the aorta the diameter is 1.0 cm. The length of the hypoplastic area is 12 cm. The renal arteries as they emerge from the aorta have quite narrow orifices, almost pin-hole on either side, slightly larger on the left. The left renal artery then dilates out again and the lumen is clear. In the right, the right renal artery is completely occluded by an adherent thrombus which is brownish-black in color.

*Urinary System:* "The right kidney weighs 140 gm. (normal weight 93 gm.), the left kidney 120 gm. (normal weight 95 gm.). The right kidney has a mottled surface consisting of deep reddish-brown colored hemorrhagic areas alternating with pale tan areas. The kidney has a soft consistency. On cut surface, the cortex is selectively hemorrhagic in a somewhat mottled fashion. The medulla is a more uniformly red-brown color. It is somewhat paler than the cortex. The pelves and ureters have a gray mucosa. The usual number of renal papillae are present. The right kidney has a pale lower pole; the upper pole is light red-brown in color. On cut surface the cortex involving the upper two-thirds of the kidney is a reddish brown color and the inferior pole is somewhat pale in color. The upper pole appears to be served by the artery previously described as containing a thrombus. There is an additional patent artery which serves the lower pole. This artery arises from the abdominal aorta about 2 cm. below the thrombosed artery."

## Comments

It is apparent that careful evaluation of the physical findings in this patient should have led to a correct diagnosis. The fact that a loud murmur was heard in the epigastric region as well as over the lower posterior chest should have alerted us to the fact that this was not a typical case of coarctation. The murmurs over the heart in abdominal coarctation are not different from those in the typical case. However, it was significant that the usual vascular type of murmur over the upper posterior chest was not heard and there was no evidence of collateral circulation. Absence of notching of the ribs was not significant as it is well known that coarctation of the thoracic aorta even to the point of complete obliteration of the lumen may occur without notching of the ribs. Bramwell and Jones[5] have pointed out, in their excellent report on the collateral circulation in coarctation of the thoracic aorta, that the third to the ninth ribs are usually involved. In abdominal coarctation, notching of the ribs is often absent but if it does occur, it involves only the lower two or three ribs. Baylin,[6] in his interesting study of the collateral circulation in a patient with obstruction of the abdominal aorta, demonstrates the origin of the murmur and the notching of the ribs. The circulation is carried on mainly by enlargement of the vessels about the celiac axis.

It might be argued that had a retrograde thoracic aortogram been recorded, we would have known that this was not a case of thoracic coarctation. This brings up the question of the advisability of aortography in all cases of coarctation of the aorta. Since the introduction of homografts, as well as plastic material, most surgeons have not felt the need of preoperative aortography as they can assess the situation during surgical exploration. It is my opinion, that because of the dangers of this procedure, aortography should be performed only in complicated instances. A number of articles have appeared in recent literature which emphasize the hazards of aortography. The literature has recently been reviewed by Koszewiski et al.[7] If a careful clinical examination is made, it should be possible to pick out the atypical cases.

## Summary

1. The physical findings in coarctation of the abdominal aorta are discussed. It is pointed out that a careful physical examination can make the diagnosis easy.

2. A case is reported in which the diagnosis was missed, resulting in an unnecessary major surgical procedure.

3. The dangers of aortography are emphasized.


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# Evaluation of a Precordial Continuous Murmur

## Rupture of Aneurysm of Sinus of Valsalva into the Right Ventricle

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A THIRTY year old man was seen with the complaint of dyspnea on effort of one year's duration. His present illness had begun thirteen months before, with severe upper abdominal pain occurring during strenuous exercise, followed by collapse and transient loss of consciousness from which he recovered spontaneously. He was kept on bedrest for thirty days but on resuming activity dyspnea on effort was noted. No history of rheumatic fever or known cardiac murmurs was obtained. The patient completed his army service without disturbances, and no cardiac abnormalities were detected on his military medical examination.

Physical examination revealed a thin young man with peculiar cervical pulsations. A positive venous pulse was present, with the characteristics of the undulating venous pulse. Carotid pulsations were strong and bounding and a water-hammer pulse was evident on forearm palpation.

Examination of the precordial region indicated cardiac enlargement, the apex beat being palpable at the sixth left intercostal space, 3 cm. beyond the nipple line. A left parasternal diffuse beat was present. Palpation revealed a continuous thrill at the fourth left intercostal space, 4 cm. to the left of the sternum. On auscultation, a loud, rough, continuous murmur with protodiastolic accentuation was heard. The second heart sound at the pulmonary area was split, both components being increased in intensity when compared with the first sound. Brachial arterial pressure was 130/65 mm. Hg.

An electrocardiogram (Fig. 1) revealed an rSR′ complex in right precordial leads, and tall R waves with depressed ST segments and diphasic (minus-plus) T waves in the left precordial leads. T wave negativity was present from leads $V_4R$ to $V_3$. Digitalis effect was also present in leads I and $V_6$. The record was interpreted as indicating biventricular hypertrophy and strain. Whether the rSR′ complex in the right precordial leads represented "incomplete right bundle branch block," late activation of the right ventricular outflow tract, or right ventricular hypertrophy was difficult to establish with the available data.

Radiologic examination revealed cardiac enlargement and pulmonary plethora in the posteroanterior position (Fig. 2a). The aortic knuckle, pulmonary artery and left lower segment were prominent. In the right anterior oblique position, right ventricular enlargement was evident and the left atrial esophageal impression was slightly prominent (Fig. 2B). In the left anterior oblique position, the left ventricular enlargement was apparent (Fig. 2C).

### DIAGNOSIS

Several diagnostic possibilities were considered. Patent ductus arteriosus was unlikely, as the position of the murmur was too

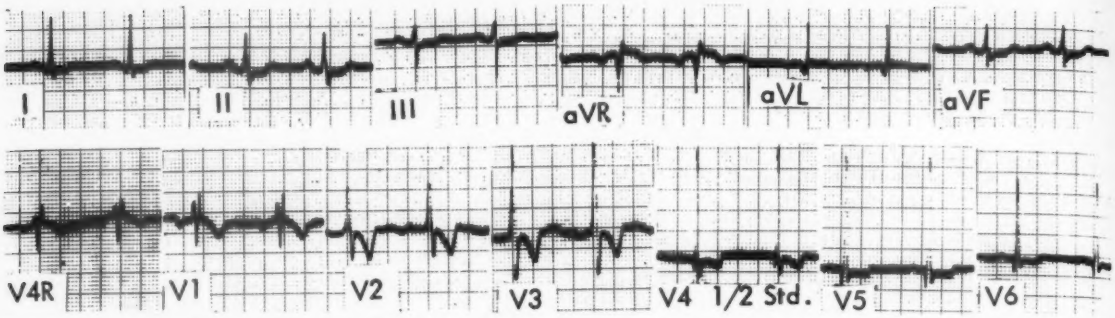



FIG. 1. Electrocardiogram showing rSR′ complex in lead $V_1$, tall R waves in lead $V_5$, and negative precordial T waves. It was interpreted as indicating biventricular hypertrophy and strain. Digitalis effect is also present.

low for this condition. Aortic-pulmonary septal defect was probable, on the basis of auscultatory signs and the peripheral pulse (Corrigan pulse). An intrathoracic arteriovenous fistula was another possibility. The previous negative medical examinations, the sudden development of upper abdominal pain and collapse one year previously, and the diastolic accentuation of the continuous murmur aroused the suspicion of a possible ruptured aortic aneurysm of the sinus of Valsalva into the right cardiac chambers.

Cardiac catheterization was performed, revealing slight elevation of the right ventricular and pulmonary arterial pressures and an increase in the oxygen content of the right ventricular outflow tract.

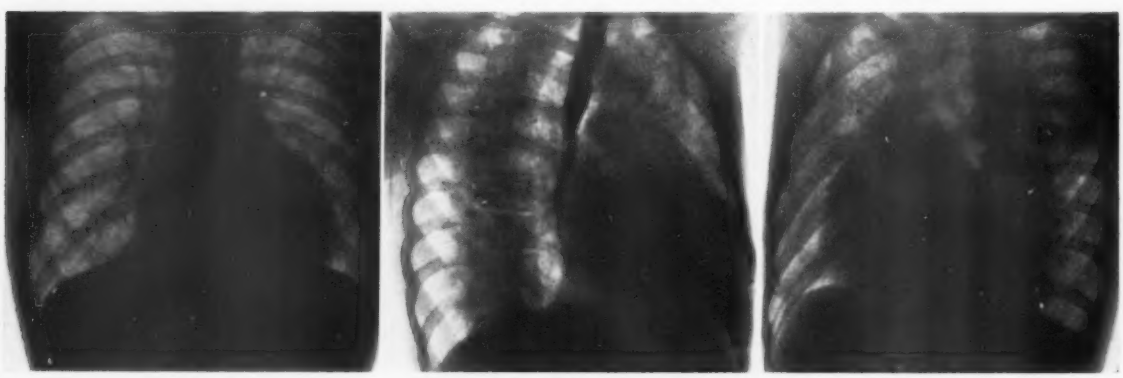
In an effort to elucidate the diagnosis further, a retrograde aortogram was performed. The pulmonary arterial trunk and ascending aorta were simultaneously visualized. On the basis of this finding the radiologist suggested an aortic-pulmonary septal defect. The history and physical examination, however, strongly indicated a ruptured aneurysm of the sinus of Valsalva into the right heart chamber. The marked cardiac enlargement and other clinical manifestations pointed to a progressive course and surgical correction seemed advisable.

*Surgical Findings:* Bilateral thoracotomy with sternal section was performed. The right atrium and ventricle were explored with a finger introduced through the right atrial appendage. An orifice of approximately 0.5 cm. in diameter between the right ventricle and aorta was found. Sutures were placed on the right ventricular wall in order to close or reduce the size of the defect.

The patient's postoperative course was uneventful except for a slight transfusion reaction. Dyspnea disappeared and cardiac enlargement diminished slightly. Physical findings and electrocardiographic abnormalities persisted.

## COMMENT

The present case shows the value of clini-



2A 2B 2C

FIG. 2. A, chest x-ray in posteroanterior position, indicating cardiac enlargement and pulmonary plethora. There is prominence of the aortic knob, pulmonary trunk and lower left contour. B, in the right anterior oblique position, the right ventricular enlargement is evident. C, in the left anterior oblique position, the left ventricular border is well over the spine, indicating enlargement of that chamber.

cal examination, since the instrumental findings employed were unable to distinguish several anatomic abnormalities which produce similar hemodynamic alterations. As retrograde aortography failed to visualize the aortic-right ventricular shunt, only dye-dilution methods would have helped to establish a definite diagnosis.

There are several points worthy of emphasis in this case: (1) The normal findings in previous examinations in the presence of a loud and rough continuous murmur which could hardly be overlooked, even by an inexperienced observer; (2) the sudden onset of upper abdominal pain, collapse and syncope, indicating the actual rupture and; (3) the combination of an undulating venous pulse, revealing tricuspid regurgitation, and arterial dance in the neck, produced by the aortic-right ventricular shunt, suggestive of this condition. The protodiastolic accentuation of the continuous murmur suggests that the maximal blood shunting was produced during this phase of the cardiac cycle, when the muscular walls encircling the abnormal communication are relaxed and the right ventricular pressure is low. All clinical data pointed against the presence of the shunt since birth, and suggested instead a ruptured aneurysm of the sinus of Valsalva which was confirmed at operation.

Readers are invited to submit reports of interesting cases and illustrative tracings for this department. These should not exceed 1,000 words in length. Although not necessarily original, all material submitted should have teaching value.

# Letter to the Editor

## Electrode Contact Fluid in Electrocardiography

Dear Sir:

Approximately ten years ago attempts were begun to minimize or overcome the disadvantages of electrocardiograph paste. This material was sticky, unpleasant and adhered alike to patient, clothing, equipment and technician. Since most of the difficulty was apparently due to the vehicle rather than its electrolyte content, various liquid formulas were prepared and tested. Eventually, an entirely suitable material was compounded of 2 per cent electrolyte in 50 per cent aqueous propenol with a small quantity of glycerine to inhibit evaporation. In use, the electrodes were moistened with the solution, applied in the normal fashion and retained with rubber straps. The tracings were recorded in the usual manner. At the conclusion of the test the electrodes were removed, drying took place promptly and the patient was able to resume his clothing without washing or delay. Electrodes were cleaned by a brief rinse in tap water.

No significant difference was detected between the records obtained with the electrode solution and those made by conventional methods. After a six-month trial period the electrode solution was adopted for routine use and has subsequently been employed for about 90 per cent of all electrocardiograms.

Recently, a commercial fluid electrode material became available.* It is supplied in 4 ounce "squeeze bottles" which permit convenient application and prevent evaporation. It appears quite similar to the solution described and is in use at this hospital. We have tested it during a three-month period and compared it with the material presently employed and with conventional electrode paste. During this time some 700 standard 12-lead electrocardiograms were made of which approximately 10 per cent were performed with electrode jelly and the remainder with the new commercial electrode solution and with the original fluid. Random selection was employed and all tracings were recorded by a single skillful technician. The records were made on four different instruments, two photographic and two "direct writing." All tracings were read by residents and reviewed by the cardiologist. When serial electrocardiograms were made on the same patient different recording technics were often employed.

It was quickly apparent that no qualitative differences existed between the three materials employed in obtaining electrode-to-skin contact. None of the readers was ever aware of the method used or of changes in technic. The records obtained by the various methods were, apparently, identical in form and in magnitude. No difference was greater than what is customarily observed over a period of time with any single method.

It was concluded that liquid electrode solutions of saline in aqueous alcohol provide adequate electrode-to-skin contact for routine electrocardiography. No significant difference was detected between tracings recorded with the use of conventional jelly, a solution prepared in the hospital pharmacy and the recently available E-Graph. However, electrode liquids are more convenient to use, cleaner and less objectionable to patients and technicians. Clothing is not soiled and patients need not wash after the test. Electrodes, especially the self-retaining variety, and instruments remain clean and corrosion is minimized.

It appears likely that presently available electrode solutions are not only adequate replacements for salt-containing electrode paste but are superior to them in many respects.

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* E-Graph, manufactured by the Hoyt Pharmaceutical Corporation, Newton, Massachusetts.

# Progress Notes in Cardiology

## Chlorothiazide and Hyperglycemia

THE EFFECTS of chlorothiazide and hydrochlorothiazide on the excretion of sodium and chloride ions are well known. However, these diuretic agents can also cause other metabolic disturbances, such as hypopotassemia, metabolic alkalosis, hyperuricemia and hyperglycemia.

The mechanism by which chlorothiazide or its analogues causes hyperglycemia is not known. It may precipitate overt diabetes in a patient who previously had latent diabetes. One patient was maintained on 32 units of lente insulin with a fasting blood sugar of 142 mg. per cent, before taking hydrochlorothiazide. Hydrochlorothiazide aggravated the diabetes and she required 94 units of lente insulin daily. Even with this massive intake of insulin, her fasting blood sugar was 206 mg. per cent. Within a week after the administration of hydrochlorothiazide was stopped, her fasting blood sugar level dropped to 166 mg. per cent. In another patient taking chlorothiazide glycosuria developed. This promptly disappeared when administration of the drug was stopped, and did not reappear when it was started again.

At the present time, I have not observed any normal patients in whom hyperglycemia developed after therapy with chlorothiazide or its derivatives.

## Readings in Cardiology

*Water Intoxication:* Water drinking is usually assumed to be harmless, and has been used by Schemm and others as a method of diuretic therapy. A normal person can drink a large amount of water without adverse effects. However, when the posterior pituitary gland is secreting an excessive amount of ADH, the ingested water will be retained. This can cause the syndrome of acute water intoxication, which is characterized clinically by the sudden development of bizarre or psychotic behavior, convulsions, hemiplegia or coma, and by a low serum sodium concentration and a decrease in the mean corpuscular hemoglobin concentration of the red blood cells. In a cardiac patient edema and an exacerbation of congestive heart failure may also develop, due to the retention of water rather than the retention of *salt* and water, which is the usual cause of cardiac edema. Excessive ADH production may occur as a result of acute stresses, such as a major operation, trauma, fear, or the intake of drugs such as Demerol® and morphine.

These and other aspects of water, electrolyte and acid-base disturbances are discussed in a monograph which has just been published.*

*Renal Tubular Necrosis:* In the past two decades physicians have learned that patients in whom acute renal tubular necrosis develops die not so much from the disease process, but as a result of excess salt and water intake, which produces pulmonary edema; or excess of water, which produces water intoxication; or hyperpotassemia, which may be due to an excessive intake of potassium-containing foods or to the acceleration of endogenous protein breakdown.

The pathological physiology, pathology, clinical diagnosis and treatment of renal tubular necrosis and related syndromes which produce oliguria and uremia have been excellently summarized in a recent book†.

*"*A Primer of Water, Electrolyte and Acid-Base Syndromes,"* by Emanuel Goldberger. Lea & Febiger, Philadelphia, 1959.

†"*Reversible Renal Insufficiency; Diagnosis and Treatment,*" by Donald H. Atlas and Peter Gaberman. The Williams and Wilkins Co., Baltimore, 1958.

*The So-Called Collagen Diseases:* We know today that collagen is not specifically involved in systemic lupus erythematosus, scleroderma, dermatomyositis, periarteritis nodosa and other so-called collagen diseases. However, this concept has stimulated an intense amount of research work in the past fifteen years and much has been learned about the connective tissue. Some of this new work is summarized in two recent books.‡

Tunbridge's book contains interesting material on the mast cells, the formation and breakdown of connective tissue and the acid mucopolysaccharides. Asboe-Hansen's book in addition, contains important clinical material on the collagen diseases and other disturbances which involve connective tissue.

‡"*Connective Tissue, A Symposium*," edited under the direction of R. E. Tunbridge. Charles C Thomas, Springfield, Ill., 1957.

"*Connective Tissue in Health and Disease*," edited by G. Absoe-Hansen. Philosophical Library, New York, 1957.

# Workmen's Compensation for the Cardiac

## Emotional Disturbance as a Cause of an Acute Cardiac Insult

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WE SHALL discuss in this paper the fourth question which the Morland Commission submitted to a number of internists and cardiologists in attempting to establish causal relationship of strain and cardiac disability.[1] The question reads as follows: "*If a workman during the course of his regular work, and where no unusual physical exertion is present, suffers a heart attack following an incident of emotional disturbance occasioned by a verbal argument with a fellow employee or the reprimand of a superior in connection with his work, from a medical viewpoint would you consider the attack as causally related to the emotional disturbance?*"

There were 376 replies to this question. Of these, 141 or 37.5 per cent said yes without reservations and 129 or 34.3 per cent believed that the relationship is possible, probable or that the emotional factor was an aggravating cause, or that infarction may be caused without occlusion of a coronary artery, or that ventricular fibrillation may result. One hundred and six physicians or 28.2 per cent said no. In other words, 270 or 71.8 per cent believed that an emotional disturbance could directly or indirectly bring about an acute "heart attack" and 106 or 28.2 per cent believed that no such causal relationship exists.

One of the major objections to the form of this question is the use of the term "heart attack." This term is so vague and all inclusive as to preclude any logical answer. In my opinion such a term should not be used by the medical profession because it does not convey any idea of what we mean by it. Does the term designate an attack of one of the tachycardias, arrhythmias, or of the anginal syndrome, or of an acute coronary occlusion, or of coronary insufficiency with myocardial ischemia, or necrosis, or of acute left heart failure with pulmonary edema, or of the onset of an acute myocardial infarction? Many physicians who answered this question rightly criticized the use of this term.

That an emotional upset may precipitate an attack of one of the tachycardias, arrhythmias and of the anginal syndrome in a susceptible person, is so well established that there can be no question. If such attacks are of transient nature leaving no structural myocardial damage in their wake, they are of no significance from a viewpoint of compensability. They should be considered merely as indications that a person presenting such disturbances may eventually have an attack severe enough to produce structural myocardial changes and should, therefore, not engage in a type of work where emotional strain is a common occurrence. From a viewpoint of avoiding compensation claims, these persons should be screened and not be accepted for a type of work which requires excessive emotional strain.

From a compensation viewpoint we are concerned with an acute onset of structural cardiac disease induced by an emotional upset, and resulting in a fatality or debilitated state of long duration and variable degree. In the vast majority of such cases there is underlying coronary atherosclerosis as discussed before[2] which was previously either undiagnosed or only suspected. We are also concerned here with in-

* Chairman, Compensation Committee, American College of Cardiology.

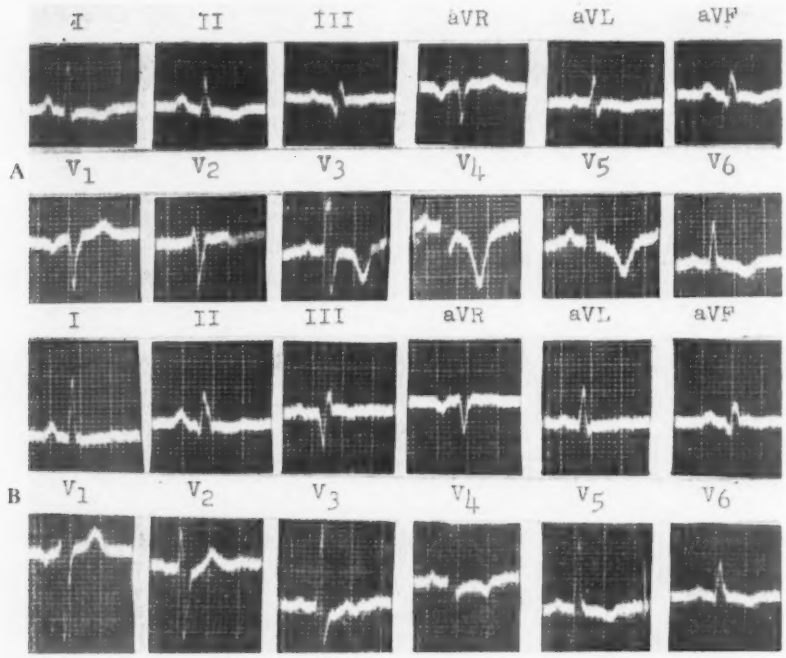


FIG. 1. A, two days after onset. Remains of old posterior wall infarction and acute ischemia of the anterior wall. B, four days after onset. Ischemia of the anterior wall of the left ventricle is greatly diminished. Evidence of previous posterior wall infarction remains the same except for larger Q wave in lead III.

stances of a sudden breakdown of the cardiovascular reserve in persons with pre-existing hypertension or valvular disease from which the patient may recover under proper treatment but in which recurrences may occur. The latter group comprises a much smaller number of cases which are easily recognizable and are usually guarded against.

### STRUCTURAL CARDIAC DAMAGE INDUCED BY EMOTION

This may consist of myocardial ischemia, ischemic necrosis or gross infarction. In the majority of cases the various processes appear to be caused by acute structural alterations in pre-existing atheromatous coronary arteries. These alterations may consist of acute intimal capillary hemorrhages, rupture of an atheromatous plaque, or the gradual onset of thrombosis induced by these changes. In some cases it may be caused by a severe acute tachycardia or arrhythmia causing insufficient filling of the coronary vessels. In some cases it appears to be due to prolonged angiospasm of a coronary artery, for an ischemic myocardial state is often observed following an emotional upset which subsides after a variable period. Also, if myocardial necrosis or infarction is found on postmortem examination in some of these cases, there may be no evidence of complete occlusion of a coronary artery to account for it.

### ILLUSTRATIVE CASE

The following case is an example of the sequence of events following an emotional upset and the resulting acute structural cardiac disease observed on autopsy.

A fifty-eight year old man, superintendent of an apartment house, had an altercation with one of the tenants. The tenant was making advances to the superintendent's wife and in his presence he told her to wash up and come up to his room to have a good time, calling her "tootsie." The superintendent became very excited and attempted to attack the tenant physically, but was restrained by some people who were there at the time. He immediately had severe pain in the anterior part of the chest with cold, clammy perspiration, and collapsed. He was removed by ambulance to a hospital.

The admission note in the hospital stated that the patient complained of constricting pain in the chest, was very pale and covered by a cold sweat. His blood pressure was 160/100 mm. Hg and the pulse rate was 100 per minute. There were moist rales at both bases of the lungs posteriorly. The heart was

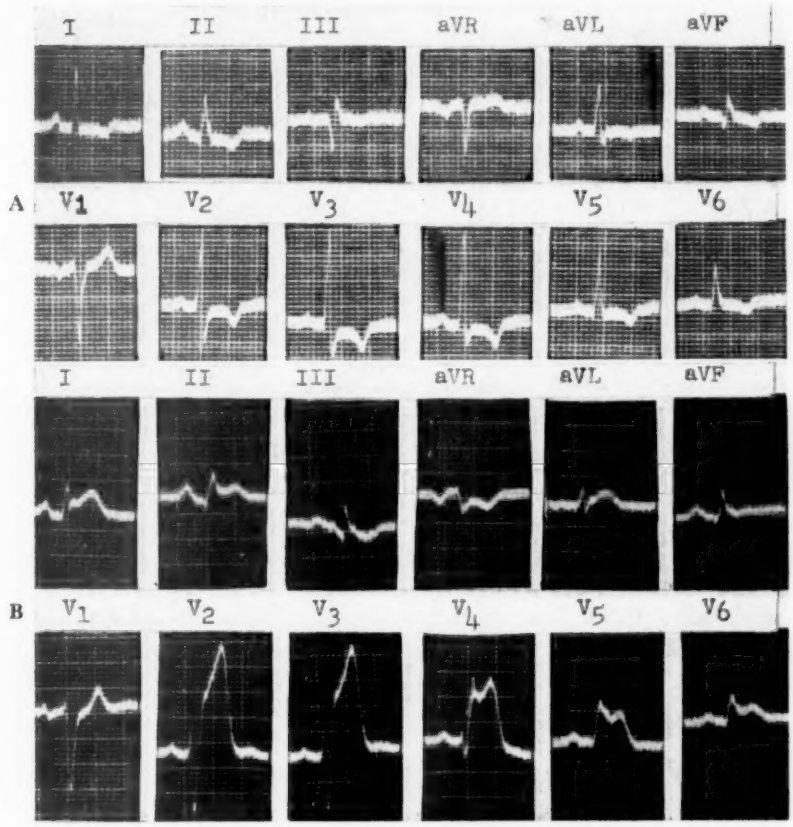


FIG. 2. A, six days after onset. Increasing myocardial ischemia of the anterior wall of the left ventricle. Signs of the old organized posterior infarct remain the same. B, nine days after onset and one day after another emotional upset. Early phase of extensive acute anteroseptal myocardial infarction extending to the anterolateral and posterior wall of the left ventricle.

not enlarged and the rhythm was regular. The abdomen showed no abnormalities, and there were no abnormal neurologic findings.

Seven years previously the patient had had an acute posterior myocardial infarction from which he made a complete clinical recovery, insofar as he was able to carry on his activities with relatively little restriction.

*Clinical Course:* The pain recurred interruptedly the following two days and was relieved to a great extent by the administration of Demerol® and morphine. The blood pressure and heart rate remained about the same, although the heart sounds improved slightly in quality. An electrocardiogram obtained on the second day of admission (Fig. 1A) showed the remains of the old posterior wall infarction, and there was evidence of acute myocardial ischemia of the anterolateral wall of the left ventricle.

The following two days the pain diminished slowly and the blood pressure was about 190/120. The patient complained of shortness of breath on and off but generally felt better. An electrocardiogram (Fig. 1B) obtained two days after the first electrocardiogram showed considerable improvement in the ischemic pattern of the anterolateral wall, but the pattern of the old organized posterior wall infarct remained the same except for a greater size of the Q wave in lead III. During the next two days the squeezing pain recurred on and off and the patient experienced considerable dyspnea. The blood pressure was high, the maximum being 205/130. An electrocardiogram (Fig. 2A) obtained two days after the second electrocardiogram showed a greater degree of myocardial ischemia of the anterior wall of the left ventricle than in Figure 1B, the signs of the old posterior wall infarction remained the same.

During the next three days the clinical findings remained about the same; he then had another emotional upset because he had to wait about one and one half hours for his evening meal and when it was brought to his bedside it was cold and unpalatable. Severe continuous pain soon developed in the chest. The following day the pain was persistent, not relieved by medication, and the patient had a cold, clammy sweat, marked ashen pallor, poor heart sounds and bilateral rales at the bases posteriorly.

His blood pressure dropped from 180/115 in the morning to 132/80 mm. Hg toward the afternoon. An electrocardiogram obtained that day (Fig. 2B) showed an early phase of extensive acute anterior wall infarction extending to the posterior wall of the left ventricle. From that day on there was a progressive downward course. The patient did not respond to any medication and died three days later.

*Autopsy* showed the following: The heart weighed 450 gm. The endocardium and myocardium showed brownish yellow discoloration over the anterior and posterior walls, septum and apex, representing about 60 per cent of the left ventricular wall. On section these areas were soft in consistency. There was a well circumscribed area of fibrosis about 3.5 cm. in diameter in the posterior wall, representing an old infarct. Both coronary ostia were moderately narrowed by yellow-white plaques and there was generalized narrowing of the lumens of the coronary arteries by atheromatosis. The main anterior descending branch of the left coronary artery was occluded by a thrombus, the distal portion of which was yellowish white. The color of the rest of the material varied from brownish translucent to purplish red. The right coronary artery also showed a fresh occlusion beginning about 4 cm. from its mouth. The circumflex branch of the left coronary artery showed an organized calcified occlusion representing the old process that occurred seven years before. Microscopic examination of the coronary arteries showed severe atherosclerosis. At sites of occlusion there were ruptured plaques with thrombosis.

## Comments

This case exemplifies the sequence of events that may follow emotional strain in a susceptible person with atherosclerosis of the coronary arteries. The early phase was that of severe acute coronary insufficiency resulting in myocardial ischemia. This was evidently caused by coronary angiospasm, subintimal hemorrhage and/or gradual development of thrombosis. In the early phases there appeared to have been some recession of the active process by the development perhaps of some collateral circulation and by the relaxation of the angiospasm. This is evidenced by the fact that the second electrocardiogram showed some improvement in the ischemic process of the myocardium. Subsequently, however, the process was accelerated again. This occurred especially during the ninth day of his stay in the hospital when he had another emotional upset, this time about his food, and complete coronary occlusion with extensive infarction soon developed.

The case history illustrates the fact that in an emotional person with pre-existing coronary disease, an acute emotional upset may change latent coronary disease to an acute active process, and during the acute process it takes only a small additional emotional upset to bring about further severe, acute activity. In fact, we do not definitely know as yet how much anxiety, emotional disturbances and fear associated with acute coronary disease contribute to the progression of the process in any case. My personal observation is that they are very important factors.

Not all cases of this kind progress to complete acute coronary occlusion and myocardial infarction. In some cases acute coronary insufficiency with myocardial ischemia occurs, lasting a variable period of days to weeks without any gross infarction. In some such cases, focal necrosis may develop; in others no evidence of destructive myocardial changes occurs.

### Mechanism

*Subintimal Hemorrhage:* The exact mechanism of the emotional effect on the production of the acute phases of coronary disease has not been fully established as yet. That it may take many days for the process to develop is evident from the case presented herein and from several other cases I have observed. Paterson[3] stresses this fact and has shown by pathologic findings in two of his cases that the factor responsible for the evolution of the process is rupture of the intimal capillaries caused by softening of the atheroma and the high intracoronary arterial pressure which is transmitted to the capillaries. This may reasonably be assumed to occur in conditions of sudden rise in aortic pressure induced by emotional strain. The resulting effects of the intimal capillary rupture in an atheromatous area is the expansion of the atheromatous plaque resulting in acute degenerative changes and gradual development of thrombosis over a period of days. In some cases rupture of a softened distended atheromatous plaque occurs with sudden onset of thrombosis.

*Changes in Coagulability of Blood:* An important additional factor in the pathogenesis of acute coronary changes under emotional disturbances is the accelerated coagulability of blood and the occurrence of other blood changes under such conditions. Many years ago, Cannon[4] had demonstrated that irritation and excitement induced experimentally in cats result in a shortening of the clotting time of the blood. Later, Izquierdo and Cannon[5] showed an increase in the red cell count occurring under similar conditions but which failed to occur when sympa-

thectomy was performed. Drayfuss[6] observed a shortened coagulation time occurring in students during examination time and Hecht[7] found in the study of blood donors that in those who were calm at the time blood was drawn, the coagulation time was normal. Among those who were apprehensive, the coagulation time was shorter and in those who were extremely apprehensive it was very short. Schneider[8] studied six cases of recurring thrombophlebitis and found that the attacks were often temporally correlated with sustained periods of emotional disturbances. Friedman and co-workers[9] have observed shortening of the clotting time and increase in the blood cholesterol in accountants during the time of the year when they worked under great strain to meet a deadline.

*Other Blood Changes:* Other changes were observed to occur during emotional stress such as an increase in the red blood cell count (mentioned herein), as well as a marked increase in the leukocyte count in dogs induced by extreme irritation and innocuous stimulation as reported by Mora and co-workers.[10] These authors also found similar changes to occur in man. They attributed the phenomenon either to a complex reaction of the involuntary nervous system or to the liberation of leukocytes from the endothelium of the blood vessels due to vascular spasm. Schottstaedt and co-workers[11] observed the loss from the body of sodium and water during a violent fright, flight, aggressive behavior, intense anger, excitement or apprehension. They attributed it to disturbances in the neurohormonal system. They believe that under normal conditions this system operates in the preservation of the individual, but under extreme emotional strain the system becomes chaotic in its behavior and harmful to the individual.

*Summary of Hemodynamic and Neurohormonal Changes:* The mechanism of an acute cardiac insult under emotional stress may thus be summarized to consist of accelerated hemodynamic changes with temporary increase in the arterial blood pressure which is transmitted to the coronary arteries and to the intimal capillaries at a site of pre-existing atheromatosis. This is probably initiated by increased activity of the adrenals via sympathetic stimulation. The process is accelerated by a shortening of blood clotting time and by hemoconcentration induced by disturbances in the neurohormonal system. Once the acute coronary process has developed it is perpetuated and becomes progressive in many cases by virtue of the acute local disease, although in many other cases it is self limited under proper management.

Those cases in which acute destructive myocardial changes occur as a result of severe prolonged tachycardia and arrhythmia induced by emotional strain, are undoubtedly caused mainly by autonomic nerve imbalance, although most of them also have the basis of an acute coronary artery insult and the other factors mentioned herein.

## Summary

An acute cardiac insult may be induced by a severe emotional upset. In most instances it occurs in persons who have underlying latent coronary atheromatosis. The acute cardiac insult in such cases consists of acute structural alterations in the atheromatous processes induced by intimal capillary hemorrhage resulting in acute reactive changes, with gradual onset of thrombosis which may end in complete occlusion and myocardial infarction after several days. In some cases sudden rupture of an atheromatous plaque may take place resulting in acute coronary thrombosis. In many cases the process may be arrested before infarction sets in. These show early the ischemic myocardial phase which abates after some time, or focal necrosis may develop.

The mechanism of the production of these pathologic processes under acute emotional strain appears to be a sudden rise in arterial blood pressure which is transmitted to the intimal capillaries causing their rupture. Additional factors are accelerated coagulability of blood and hemoconcentration occurring under emotional strain, as well as coronary angiospasm.

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# College News

## EIGHTH INTERIM MEETING

AMERICAN COLLEGE OF CARDIOLOGY

Benjamin Franklin Hotel, Philadelphia, Pennsylvania

October 23 to 25, 1959

# Scientific Program

### Fireside Conferences

*Friday, October 23, 1959, 8:30 to 10:30 P.M.*

Diagnosis and Treatment of Arrhythmias.
SAMUEL BELLET, M.D.
Philadelphia, Pa.
DAVID SCHERF, M.D.
New York, N. Y.

Respirocardiac Failure.
DAVID B. DILL, M.D.
Army Chemical Center, Md.
GEORGE F. MENEELY, M.D.
Nashville, Tenn.

Office Diagnosis of Congenital Heart Disease.
BENJAMIN M. GASUL, M.D.
Chicago, Ill.
HENRY A. ZIMMERMAN, M.D.
Cleveland, Ohio.

Use and Abuse of Digitalis.
ARTHUR C. DE GRAFF, M.D.
New York, N. Y.
E. GREY DIMOND, M.D.
Kansas City, Kans.
SAMUEL A. LEVINE, M.D.
Boston, Mass.

Present Status of Clot Lysis.
ALVIN H. FREIMAN, M.D.
New York, N. Y.
ALAN J. JOHNSON, M.D.
New York, N. Y.

Anticoagulant Treatment of Cerebrovascular Disease.
CLARK H. MILLIKAN, M.D.
Rochester, Minn.
IRVING S. WRIGHT, M.D.
New York, N. Y.

Anticoagulant Therapy in Heart and Peripheral Vascular Disease.
E. STERLING NICHOL, M.D.
Miami, Fla.
HENRY I. RUSSEK, M.D.
Staten Island, N. Y.

Diet and Atherosclerosis.
EDWARD H. AHRENS, JR., M.D.
New York, N. Y.
LOUIS N. KATZ, M.D.
Chicago, Ill.

Selection of Patients for Artery Replacement.
MICHAEL E. DE BAKEY, M.D.
Houston, Tex.
ORMAND C. JULIAN, M.D.
Chicago, Ill.

Use of Enzymes in Diagnosis of Heart Disease.
CLARENCE M. AGRESS, M.D.
Los Angeles, Calif.
JOHN S. LADUE, M.D.
New York, N. Y.

Present-Day Management of Hypertension.
B. L. MARTZ, M.D.
Indianapolis, Ind.
JOHN H. MOYER, M.D.
Philadelphia, Pa.

Current Practice in Prophylaxis and Treatment of Acute Rheumatic Fever.
BENEDICT F. MASSELL, M.D.
Boston, Mass.
SIDNEY ROTHBARD, M.D.
New York, N. Y.
MILTON S. SASLAW, M.D.
Miami, Fla.

Monamine Oxidase Inhibitors.
GEORGE C. GRIFFITH, M.D.
Los Angeles, Calif.
GERHARD ZBINDEN, M.D.
Nutley, N. J.

Treatment of Refractory Heart Failure.
SIMON DACK, M.D.
New York, N. Y.
LOUIS LEITER, M.D.
New York, N. Y.

The Myocarditides.
EDGAR HULL, M.D.
New Orleans, La.
WILLIAM H. WEHRMACHER, M.D.
Chicago, Ill.

Valvular Replacement.
CHARLES P. BAILEY, M.D.
Philadelphia, Pa.
EARLE B. KAY, M.D.
Cleveland, Ohio.

## Symposium on Cardiac Resuscitation

*Sunday, October 25, 1959, 2:00 to 4:00 P.M.*

*Moderators:* OSLER A. ABBOTT, M.D.
Atlanta, Ga.
ERNEST CRAIGE, M.D.
Chapel Hill, N. C.

Presentation of the Problem.
J. WILLIS HURST, M.D.
Atlanta, Ga.

Extracardiac Pacemakers and External Defibrillation.
PAUL M. ZOLL, M.D.
Boston, Mass.

Prevention and Recognition of Cardiac Arrest from the Viewpoint of the Anesthetist.
PALUEL J. FLAGG, M.D.
New York, N. Y.

Surgical Resuscitation of the Heart.
CLAUDE S. BECK, M.D.
Cleveland, Ohio.

Hypothermia as an Adjunct to Cardiac Resuscitation.
FRANK SPENCER, M.D.
Baltimore, Md.

Summary and Discussion: Surgical Aspects.
OSLER A. ABBOTT, M.D.
Atlanta, Ga.

Medical Aspects.
ERNEST CRAIGE, M.D.
Chapel Hill, N. C.

## Symposium on Mechanical Methods of Assistance to the Failing Circulation

*Sunday, October 25, 1959, 4:15 to 5:00 P.M.*

*Moderator:* OSLER A. ABBOTT, M.D.
Atlanta, Ga.

Effects of Mechanical Assistance upon Normal and Failing Hearts.
PETER F. SALISBURY, M.D.
Burbank, Calif.

Physiologic Principles of Partial Extracorporeal Circulation.
PIERRE M. GALLETTI, M.D.
Lausanne, Switzerland.

Clinical Application of Mechanical Assistance to the Failing Heart.
DWIGHT E. HARKEN, M.D.
Boston, Mass.

# General Convention Schedule

*Thursday, October 22, 1959*

5:00 P.M.–11:00 P.M.
85th Board of Trustees Dinner Meeting
Valley Forge Room

*Friday, October 23, 1959*

9:00 A.M.–5:00 P.M.
Scientific Program—American Heart Association, Philadelphia Convention Hall

NOON–8:00 P.M.
Registration—A.C.C.—Mezzanine Floor—Benjamin Franklin

*Saturday, October 24, 1959*

8:00 A.M.–4:00 P.M.
Registration—A.C.C.—Mezzanine Floor—Benjamin Franklin

9:00 A.M.—5:00 P.M.
Scientific Program—American Heart Association, Convention Hall

*Sunday, October 25, 1959*

10:00 A.M.–2:00 P.M.
Registration—A.C.C.—Mezzanine Floor—Benjamin Franklin

9:00 A.M.–12:30 P.M.
Scientific Program—American Heart Association, Convention Hall

2:00 P.M.–5:00 P.M.
Scientific Program, Convention Hall